ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

PegIntron 50 micrograms powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of PegIntron, powder for solution for injection contains 50 micrograms of peginterferon alfa-2b as measured on a protein basis.
Each vial provides 50 micrograms/0.5 ml of peginterferon alfa-2b when reconstituted as recommended.

The active substance is a covalent conjugate of recombinant interferon alfa-2b* with monomethoxy polyethylene glycol. The potency of this product should not be compared to that of another pegylated or non-pegylated protein of the same therapeutic class. For more information, see section **5.1.**
*produced by rDNA technology in *E.coli* cells harbouring a genetically engineered plasmid hybrid encompassing an interferon alfa-2b gene from human leukocytes

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection
The white powder is contained in a 2 ml glass vial and the clear and colourless solvent is presented in a 2 ml glass ampoule.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PegIntron is indicated for the treatment of adult patients with chronic hepatitis C who have elevated transaminases without liver decompensation and who are positive for serum HCV-RNA or anti-HCV (see section **4.4**).

The best way to use PegIntron in this indication is in combination with ribavirin.

This combination is indicated in naïve patients as well as in patients who have previously responded (with normalisation of ALT at the end of treatment) to interferon alpha monotherapy but who have subsequently relapsed.

Interferon monotherapy, including PegIntron, is indicated mainly in case of intolerance or contraindication to ribavirin.

Please refer also to the ribavirin Summary of Product Characteristics (SPC) when PegIntron is to be used in combination with ribavirin.

4.2 Posology and method of administration

Treatment should be initiated and monitored only by a physician experienced in the management of patients with hepatitis C.

Dose to be administered
PegIntron should be administered as a once weekly subcutaneous injection. The dose administered depends on whether it is used in combination with ribavirin or as monotherapy.

Combination therapy
PegIntron 1.5 micrograms/kg/week in combination with ribavirin capsules.

The intended dose of 1.5 μg/kg of PegIntron to be used in combination with ribavirin may be delivered in weight categories with the pen/vial strengths according to **Table 1**. Ribavirin capsules are to be administered orally each day in two divided doses with food (morning and evening).

Table 1 - Dosing for Combination Therapy

Body Weight (kg)	PegIntron		Ribavirin Capsules	
	Vial/Pen Strength (μg/0.5ml)	Administer Once Weekly (ml)	Total Daily Dose (mg)	Number of Capsules (200 mg)
< 40	50	0.5	800	4[a]
40-50	80	0.4	800	4[a]
51-64	80	0.5	800	4[a]
65-75	100	0.5	1,000	5[b]
76-85	120	0.5	1,000	5[b]
> 85	150	0.5	1,200	6[c]

a: 2 morning, 2 evening
b: 2 morning, 3 evening
c: 3 morning, 3 evening

Duration of treatment
Predictability of sustained virological response: Patients infected with virus genotype 1 who fail to achieve virological response at Week 12 are highly unlikely to become sustained virological responders (see also section **5.1**).

- **Genotype 1**: For patients who exhibit virological response at week 12, treatment should be continued for another nine month period (i.e., a total of 48 weeks).
- **Genotypes 2 or 3**: It is recommended that all patients be treated for 24 weeks.
- **Genotype 4:** In general, patients infected with genotype 4 are considered harder to treat and limited study data (n=66) indicate they are compatible with a posology as for genotype 1.

PegIntron monotherapy
As monotherapy the PegIntron regimen is 0.5 or 1.0 microgram/kg/week. The lowest vial or pen strength available is 50 μg/0.5 ml; therefore for patients prescribed 0.5 μg/kg/week, doses must be adjusted by volume as shown in **Table 2**. For the 1.0 μg/kg dose, similar volume adjustments can be made or alternate vial strengths can be used as shown in **Table 2**.

Table 2- Monotherapy Dosing

	0.5 μg/kg		1.0 μg/kg	
Body Weight (kg)	Vial/Pen Strength (μg/0.5ml)	Administer Once Weekly (ml)	Vial/Pen Strength (μg/0.5ml)	Administer Once Weekly (ml)
30-35	50*	0.15	50	0.3
36-45	50*	0.2	50	0.4
46-56	50*	0.25	50	0.5
57-72	50	0.3	80	0.4
73-88	50	0.4	80	0.5

89-106	50	0.5	100	0.5
> 106**	80	0.4	120	0.5
* Must use vial. Minimum delivery for pen is 0.3 ml. ** For patients > 120 kg, use 80 µg/0.5 ml vial				

Duration of treatment
For patients who exhibit virological response at Week 12, treatment should be continued for at least another three-month period (i.e., a total of six months). The decision to extend therapy to one year of treatment should be based on prognostic factors (e.g., genotype, age > 40 years, male gender, bridging fibrosis).

Dose modification for all patients
If severe adverse reactions or laboratory abnormalities develop during treatment with PegIntron monotherapy or PegIntron in combination with ribavirin, modify the dosages of each product as appropriate, until the adverse reactions abate. Guidelines were developed in clinical trials for dose modification.

Combination Therapy Dose Reduction Guidelines

Table 2a Dose modification guidelines for combination therapy (with ribavirin)

Laboratory values	**Reduce only ribavirin dose to 600 mg/day* if:**	**Reduce only PegIntron dose to one-half dose if:**	**Discontinue combination therapy if:**
Haemoglobin	< 10 g/dl	-	< 8.5 g/dl
Haemoglobin in: Patients with history of stable cardiac disease	≥ 2 g/dl decrease in haemoglobin during any four week period during treatment (permanent dose reduction)		< 12 g/dl after four weeks of dose reduction
White blood cells	-	< 1.5 x 10^9/l	< 1.0 x 10^9/l
Neutrophils	-	< 0.75 x 10^9/l	< 0.5 x 10^9/l
Platelets	-	< 50 x 10^9/l	< 25 x 10^9/l
Bilirubin – direct	-	-	2.5 x ULN**
Bilirubin - indirect	> 5 mg/dl	-	> 4 mg/dl (for > 4 weeks)
Creatinine	-	-	> 2.0 mg/dl
ALT/AST	-	-	2 x baseline and > 10 x ULN**

* Patients whose dose of ribavirin is reduced to 600 mg daily receive one 200 mg capsule in the morning and two 200 mg capsules in the evening.

** Upper limit of normal

Dose reduction of PegIntron may be accomplished by either reducing the prescribed volume by one-half or by utilizing a lower dose strength as shown in **Table 2b**.

Table 2b – Reduced PegIntron Dosing for Combination Therapy

Body Weight (kg)	**Target Reduced Dose (µg)**	**Vial/Pen Strength (µg/0.5 ml)**	**Administer Once Weekly (ml)**	**Amount Delivered (µg)**
< 40	25	50*	0.25	25
40-50	32	50	0.3	30
51-64	40	50	0.4	40
65-75	50	50	0.5	50

76-85	60	80	0.4	64
> 85	75	100	0.4	80
*Must use vial. Minimum delivery for pen is 0.3 ml.				

PegIntron Monotherapy Dose Reduction Guidelines

Dose modification guidelines for patients who use PegIntron monotherapy are shown in **Table 3a.**

Table 3a Dose modification guidelines for PegIntron monotherapy		
Laboratory values	**Reduce PegIntron to one-half dose if:**	**Discontinue PegIntron if:**
Neutrophils	< 0.75 x 10^9/l	< 0.5 x 10^9/l
Platelets	< 50 x 10^9/l	< 25 x 10^9/l

Dose reduction for patients who use 0.5 µg/kg PegIntron monotherapy must be accomplished by reducing the prescribed volume by one-half. The 50 µg/0.5 ml vial must be used if necessary since the pen can only deliver a minimum volume of 0.3 ml.

For patients who use 1.0 µg/kg PegIntron monotherapy, dose reduction may be accomplished by reducing the prescribed volume by one-half or by utilizing a lower dose strength as shown in **Table 3b**.

Table 3b – Reduced PegIntron Dose for the 1.0 µg/kg Monotherapy Regimen				
Body Weight (kg)	**Target Reduced Dose (µg)**	**Vial/Pen Strength (µg/0.5ml)**	**Administer Once Weekly (ml)**	**Amount Delivered (µg)**
30-35	15	50*	0.15	15
36-45	20	50*	0.20	20
46-56	25	50*	0.25	25
57-72	32	50	0.3	30
73-89	40	50	0.4	40
90-106	50	50	0.5	50
> 106	60	80	0.4	64
*Must use vial. Minimum delivery for pen is 0.3 ml.				

Special populations

Use in renal impairment: The clearance of PegIntron is reduced in patients with significant renal impairment. Patients with creatinine clearance ≤ 50 ml/minute must not be treated with PegIntron (see section **5.2**). It is recommended that patients with moderate renal impairment be closely monitored and that their weekly dose of PegIntron be reduced if medically appropriate.

Use in hepatic impairment: The safety and efficacy of PegIntron therapy has not been evaluated in patients with severe hepatic dysfunction, therefore PegIntron must not be used for these patients.

Use in the elderly (≥ 65 years of age): There are no apparent age-related effects on the pharmacokinetics of PegIntron. Data from elderly patients treated with a single dose of PegIntron suggest no alteration in PegIntron dose is necessary based on age (see section **5.2**).

Use in patients under the age of 18 years: PegIntron is not recommended for use in children or adolescents under the age of 18, as there is no experience in this group.

4.3 Contraindications

- Hypersensitivity to the active substance or to any interferon or to any of the excipients;
- Pregnant women;
- Women who are breast-feeding;
- A history of severe pre-existing cardiac disease, including unstable or uncontrolled cardiac disease in the previous six months (see section **4.4**);
- Severe, debilitating medical conditions, including patients with chronic renal failure or creatinine clearance < 50 ml/minute;
- Autoimmune hepatitis or a history of autoimmune disease;
- Severe hepatic dysfunction or decompensated cirrhosis of the liver;
- Pre-existing thyroid disease unless it can be controlled with conventional treatment;
- Epilepsy and/or compromised central nervous system (CNS) function.

4.4 Special warnings and special precautions for use

There is no experience with PegIntron in combination with ribavirin in patients who have relapsed after interferon alpha + ribavirin therapy.

All patients in the chronic hepatitis C studies had a liver biopsy before inclusion, but in certain cases (i.e. patients with genotype 2 and 3), treatment may be possible without histological confirmation. Current treatment guidelines should be consulted as to whether a liver biopsy is needed prior to commencing treatment.

Acute hypersensitivity: Acute hypersensitivity reactions (e.g., urticaria, angioedema, bronchoconstriction, anaphylaxis) have been observed rarely during interferon alfa-2b therapy. If such a reaction develops during treatment with PegIntron, discontinue treatment and institute appropriate medical therapy immediately. Transient rashes do not necessitate interruption of treatment.

Cardiovascular system: As with interferon alfa-2b, patients with a history of congestive heart failure, myocardial infarction and/or previous or current arrhythmic disorders, receiving PegIntron therapy require close monitoring. It is recommended that patients who have pre-existing cardiac abnormalities have electrocardiograms taken prior to and during the course of treatment. Cardiac arrhythmias (primarily supraventricular) usually respond to conventional therapy but may require discontinuation of PegIntron therapy.

Psychiatric and Central Nervous System (CNS): If treatment with peginterferon alfa-2b is judged necessary in patients with existence or history of severe psychiatric conditions, this should only be initiated after having ensured appropriate individualised diagnostic and therapeutic management of the psychiatric condition.
Severe CNS effects, particularly depression, suicidal ideation and attempted suicide have been observed in some patients during PegIntron therapy. Other CNS effects including aggressive behaviour, confusion and alterations of mental status have been observed with alpha interferon. If patients develop psychiatric or CNS problems, including clinical depression, it is recommended that the patient be carefully monitored due to the potential seriousness of these undesirable effects. If symptoms persist or worsen, discontinue PegIntron therapy.
More significant obtundation and coma, including cases of encephalopathy, have been observed in some patients, usually elderly, treated at higher doses for oncology indications. While these effects are generally reversible, in a few patients full resolution took up to three weeks. Very rarely, seizures have occurred with high doses of interferon alpha.

Liver function: As with all interferons, discontinue treatment with PegIntron in patients who develop prolongation of coagulation markers which might indicate liver decompensation.

Fever: While fever may be associated with the flu-like syndrome reported commonly during interferon therapy, other causes of persistent fever must be ruled out.

Hydration: Adequate hydration must be maintained in patients undergoing PegIntron therapy since hypotension related to fluid depletion has been seen in some patients treated with alpha interferons. Fluid replacement may be necessary.

Pulmonary changes: Pulmonary infiltrates, pneumonitis, and pneumonia, occasionally resulting in fatality, have been observed rarely in interferon alpha treated patients. Any patient developing fever, cough, dyspnea or other respiratory symptoms must have a chest X-ray taken. If the chest X-ray shows pulmonary infiltrates or there is evidence of pulmonary function impairment, the patient is to be monitored closely, and, if appropriate, discontinue interferon alpha. Prompt discontinuation of interferon alpha administration and treatment with corticosteroids appear to be associated with resolution of pulmonary adverse events.

Autoimmune disease: The development of auto-antibodies and autoimmune disorders has been reported during treatment with alpha interferons. Patients predisposed to the development of autoimmune disorders may be at increased risk. Patients with signs or symptoms compatible with autoimmune disorders should be evaluated carefully, and the benefit-risk of continued interferon therapy should be reassessed (see also section **4.4 Thyroid changes** and **4.8**).

Ocular changes: Ophthalmologic disorders, including retinal haemorrhages, cotton wool spots, and retinal artery or vein obstruction have been reported in rare instances after treatment with alpha interferons (see section **4.8**). All patients should have a baseline eye examination. Any patient complaining of ocular symptoms, including loss of visual acuity or visual field must have a prompt and complete eye examination. Periodic visual examinations are recommended during PegIntron therapy, particularly in patients with disorders that may be associated with retinopathy, such as diabetes mellitus or hypertension. Discontinuation of PegIntron should be considered in patients who develop new or worsening ophthalmological disorders.

Thyroid changes: Infrequently, patients treated for chronic hepatitis C with interferon alpha have developed thyroid abnormalities, either hypothyroidism or hyperthyroidism. Determine thyroid stimulating hormone (TSH) levels if, during the course of therapy, a patient develops symptoms consistent with possible thyroid dysfunction. In the presence of thyroid dysfunction, PegIntron treatment may be continued if TSH levels can be maintained in the normal range by medication.

Metabolic disturbances: Hypertriglyceridemia and aggravation of hypertriglyceridemia, sometimes severe, have been observed. Monitoring of lipid levels is, therefore, recommended.

HCV/HIV Coinfection
Patients co-infected with HIV and receiving Highly Active Anti-Retroviral Therapy (HAART) may be at increased risk of developing lactic acidosis. Caution should be used when adding PegIntron and ribavirin to HAART therapy (see ribavirin SPC).
Co-infected patients with advanced cirrhosis receiving HAART may be at increased risk of hepatic decompensation and death. Adding treatment with alfa interferons alone or in combination with ribavirin may increase the risk in this patient subset.

Organ transplant recipients: The safety and efficacy of PegIntron alone or in combination with ribavirin for the treatment of hepatitis C in liver or other organ transplant recipients have not been studied. Preliminary data indicates that interferon alpha therapy may be associated with an increased rate of kidney graft rejection. Liver graft rejection has also been reported.

Other: Due to reports of interferon alpha exacerbating pre-existing psoriatic disease and sarcoidosis, use of PegIntron in patients with psoriasis or sarcoidosis is recommended only if the potential benefit justifies the potential risk.

Laboratory tests: Standard haematologic tests, blood chemistry and a test of thyroid function must be conducted in all patients prior to initiating therapy. Acceptable baseline values that may be considered as a guideline prior to initiation of PegIntron therapy are:

- Platelets ≥ 100,000/mm^3
- Neutrophil count ≥ 1,500/mm^3
- TSH level must be within normal limits

Laboratory evaluations are to be conducted at weeks 2 and 4 of therapy, and periodically thereafter as clinically appropriate.

4.5 Interaction with other medicinal products and other forms of interaction

Results of a single-dose study with PegIntron demonstrated no effect on the activity of cytochrome (CY) P1A2, CYP2C8/9, CYP2D6, and hepatic CYP3A4 or N-acetyl transferase. Caution should be advised in the interpretation of these results as the use of other forms of interferon alpha result in a 50 % reduction in the clearance and thus a doubling of plasma concentrations of theophylline, a substrate of CYP1A2.

No pharmacokinetic interactions were noted between PegIntron and ribavirin in a multiple-dose pharmacokinetic study.

4.6 Pregnancy and lactation

There are no adequate data on the use of interferon alfa-2b in pregnant women. Interferon alfa-2b has been shown to be abortifacient in primates. PegIntron is likely to also cause this effect. PegIntron should not be used during pregnancy (see section **5.3**).

PegIntron is recommended for use in fertile women only when they are using effective contraception during the treatment period.

Lactation: It is not known whether the components of this medicinal product are excreted in human milk. Because of the potential for adverse reactions in nursing infants, nursing must be discontinued prior to initiation of treatment.

Ribavirin is teratogenic and embryocidal and must not be used in pregnant women (see ribavirin SPC, **5.3**).

4.7 Effects on ability to drive and use machines

Patients who develop fatigue, somnolence or confusion during treatment with PegIntron are cautioned to avoid driving or operating machinery.

4.8 Undesirable effects

The safety of PegIntron is evaluated from data from two clinical trials: one with PegIntron monotherapy, one with PegIntron in combination with ribavirin. In both cases, patients were treated for one year.

Table 4 describes the regimens and patient exposure for one year of treatment in patients with no previous exposure to interferon (interferon-naïve patients). Because of a significant overlap in the pattern of undesirable effects with PegIntron monotherapy, groups of patients have been brought together in **Table 5** to show the pattern of reported effects for all monotherapy groups.

Table 4	Regimens and patient exposure	
Treatment	**Regimen**	**Number of patients treated for one year**
PegIntron + ribavirin	PegIntron (1.5 micrograms/kg/week) + ribavirin (> 10.6 mg/kg/day)	188
Interferon alfa-2b + ribavirin	Interferon alfa-2b (3 MIU three times a week) + ribavirin (1,000/1,200 mg/day)	505
PegIntron monotherapy	PegIntron (0.5 microgram/kg/week)	315
	PegIntron (1.0 microgram/kg/week)	297
	PegIntron (1.5 micrograms/kg/week)	304

Table 5 Undesirable effects reported in clinical trials (≥ 10 % of patients in PegIntron + ribavirin group)			
	PegIntron + ribavirin	**Interferon alfa-2b + ribavirin**	**PegIntron monotherapy**
Application site disorder			
Injection site inflammation	20 %	17 %	39-44 %
Injection site reaction	54 %	36 %	7-9 %
Body as a whole			
Headache	58 %	57 %	57-63 %
Fatigue	56 %	59 %	43 %
Rigors	42 %	40 %	33-43 %
Fever	39 %	32 %	29-43 %
Flu-like symptoms	21 %	23 %	18-25 %
Asthenia	28 %	17 %	12-14 %
Weight decrease	30 %	19 %	8-18 %
Gastrointestinal			
Nausea	43 %	31 %	20-23 %
Anorexia	35 %	26 %	10-25 %
Diarrhoea	20 %	13 %	14-17 %
Abdominal pain	12 %	9 %	11 %
Vomiting	16 %	10 %	4-7 %
Musculoskeletal			
Myalgia	49 %	49 %	46-60 %
Arthralgia	31 %	26 %	23-28 %
Musculoskeletal pain	15 %	11 %	11-13 %
Psychiatric			
Depression	34 %	32 %	26 %
Irritability	32 %	34 %	19 %
Insomnia	37 %	41 %	16-19 %
Anxiety	14 %	14 %	8 %
Concentration impaired	18 %	21 %	9-10 %
Emotional lability	11 %	10 %	5 %
Respiratory system			
Pharyngitis	10 %	7 %	3 %
Coughing	14 %	11 %	4 %
Dyspnea	26 %	22 %	5 %
Skin and appendages			
Alopecia	45 %	32 %	20-34 %
Pruritus	27 %	27 %	7-9 %
Skin dry	23 %	21 %	6-9 %
Rash	21 %	21 %	5-7 %
Other			
Dizziness	17 %	16 %	7-12 %
Infection viral	10 %	5 %	4-5 %
Mouth dry	10 %	8 %	4-8 %

Table 6 Undesirable effects reported in clinical trials (1%-< 10% of patients treated with PegIntron + ribavirin or PegIntron monotherapy)		
Body system	**5-10%**	**1-<5%**
Body as a whole	chest pain, RUQ pain, malaise	erythema, injection site pain, flushing, thirst, herpes simplex, face or peripheral oedema, dehydration
Cardiovascular		tachycardia, palpitation, hypotension, hypertension, syncope
Central/peripheral nervous system	paresthesia	hypoaesthesia, hyperaesthesia, hypertonia, decreased libido, confusion, tremor, vertigo, migraine, tinnitus, hearing impairment/loss, ataxia, neuralgia
Endocrine	hypothyroidism,	hyperthyroidism, amenorrhoea, prostatitis, hyperuricemia, hypocalcemia
Gastrointestinal	dyspepsia,	constipation, taste perversion, loose stools, stomatitis, ulcerative stomatitis, gingival bleeding, glossitis, flatulence, hemorrhoids, gastroesophageal reflux, hepatomegaly, bilirubinemia, gingivitis
Haematologic	anaemia, leukopaenia	thrombocytopenia, lymphadenopathy,
Musculoskeletal		arthritis
Ocular		blurred vision, conjunctivitis, lacrimal gland disorder, eye pain
Psychiatric	agitation, nervousness	aggressive behaviour, somnolence, behavior disorder, apathy, appetite increased, sleep disorder, dreaming abnormal
Reproductive	menstrual disorder, menorrhagia	ovarian disorder, vaginal disorder, sexual dysfunction (not specified), impotence, breast pain
Respiratory		nonproductive cough, rhinitis, sinusitis, bronchitis, respiratory disorder, nasal congestion, rhinorrhea, dysphonia, epistaxis
Resistance mechanism		otitis media, fungal infection, bacterial infection
Skin and appendages	increased sweating	erythematous rash, eczema, photosensitivity reaction, maculopapular rash, abnormal hair texture, acne, dermatitis, furunculosis, nail disorder, psoriasis, urticaria
Urinary		micturition frequency, urine abnormal

Most cases of neutropaenia and thrombocytopaenia were mild (WHO grades 1 or 2). There were some cases of more severe neutropenia in patients treated with the recommended doses of PegIntron in combination with ribavirin (WHO grade 3: 39 of 186 [21 %]; and WHO grade 4: 13 of 186 [7 %]).

In a clinical trial, approximately 1.2 % of patients treated with PegIntron or interferon alfa-2b in combination with ribavirin reported life-threatening psychiatric events during treatment. These events included suicidal ideation and attempted suicide (see section **4.4)**. Following marketing, psychosis and hallucination have been reported rarely.

Rarely reported events with interferon alfa-2b, including PegIntron, include seizure, pancreatitis, arrhythmia, peripheral neuropathy, diabetes, rhabdomyolysis, myositis, renal insufficiency and renal failure.

Cardiovascular (CVS) adverse events, particularly arrhythmia, appeared to be correlated mostly with pre-existing CVS disease and prior therapy with cardiotoxic agents (see section **4.4**). Cardiomyopathy, that may be reversible upon discontinuation of interferon alpha, has been reported rarely in patients without prior evidence of cardiac disease.

Very rarely cases of erythema multiforme, Stevens Johnson syndrome, toxic epidermal necrolysis, cardiac ischaemia, myocardial infarction, cerebrovascular ischaemia, cerebrovascular hemorrhage, encephalopathy, sarcoidosis or exacerbation of sarcoidosis, interstitial lung disease and injection site necrosis have been reported. Ulcerative and ischaemic colitis have been reported very rarely with PegIntron.

Very rarely, interferon alfa-2b or PegIntron used alone or in combination with ribavirin may be associated with aplastic anaemia.

Ophthalmological disorders that have been reported rarely with alpha interferons include retinopathies (including macular oedema), retinal haemorrhages, retinal artery or vein obstruction, cotton wool spots, loss of visual acuity or visual field, optic neuritis, and papilloedema (see section **4.4**).

A wide variety of autoimmune and immune-mediated disorders have been reported with alpha interferons including thyroid disorders, idiopathic and thrombotic thrombocytopenic purpura, vasculitis, neuropathies including mononeuropathies (see also section **4.4**, **Autoimmune disorders**).

4.9 Overdose

In clinical trials, cases of accidental overdose, at never more than twice the prescribed dose, were reported. There were no serious reactions. Undesirable effects resolved during continued administration of PegIntron.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunostimulants, Cytokines and immunomodulators, Interferons, Peginterferon alfa-2b, ATC code: L03A B10.

Recombinant interferon alfa-2b is covalently conjugated with monomethoxy polyethylene glycol at an average degree of substitution of 1 mole of polymer/mole of protein. The average molecular mass is approximately 31,300 daltons of which the protein moiety constitutes approximately 19,300.

Interferon alfa-2b
In vitro and *in vivo* studies suggest that the biological activity of PegIntron is derived from its interferon alfa-2b moiety.

Interferons exert their cellular activities by binding to specific membrane receptors on the cell surface. Studies with other interferons have demonstrated species specificity. However, certain monkey species, e.g., Rhesus monkeys, are susceptible to pharmacodynamic stimulation upon exposure to human type 1 interferons.

Once bound to the cell membrane, interferon initiates a complex sequence of intracellular events that include the induction of certain enzymes. It is thought that this process, at least in part, is responsible for the various cellular responses to interferon, including inhibition of virus replication in virus-infected cells, suppression of cell proliferation and such immunomodulating activities as enhancement

of the phagocytic activity of macrophages and augmentation of the specific cytotoxicity of lymphocytes for target cells. Any or all of these activities may contribute to interferon's therapeutic effects.

Recombinant interferon alfa-2b also inhibits viral replication *in vitro* and *in vivo*. Although the exact antiviral mode of action of recombinant interferon alfa-2b is unknown, it appears to alter the host cell metabolism. This action inhibits viral replication or if replication occurs, the progeny virions are unable to leave the cell.

PegIntron
PegIntron pharmacodynamics were assessed in a rising single-dose trial in healthy subjects by examining changes in oral temperature, concentrations of effector proteins such as serum neopterin and 2'5'-oligoadenylate synthetase (2'5'-OAS), as well as white cell and neutrophil counts. Subjects treated with PegIntron showed mild dose-related elevations in body temperature. Following single doses of PegIntron between 0.25 and 2.0 micrograms/kg/week, serum neopterin concentration was increased in a dose-related manner. Neutrophil and white cell count reductions at the end of week 4 correlated with the dose of PegIntron.

PegIntron clinical trials
Two pivotal trials have been conducted, one (C/I97-010) with PegIntron monotherapy; the other (C/I98-580) with PegIntron in combination with ribavirin. Eligible patients for these trials had chronic hepatitis C confirmed by a positive HCV-RNA polymerase chain reaction (PCR) assay (> 30 IU/ml), a liver biopsy consistent with a histological diagnosis of chronic hepatitis with no other cause for the chronic hepatitis, and abnormal serum ALT.

In the PegIntron monotherapy trial, a total of 916 naïve chronic hepatitis C patients were treated with PegIntron (0.5, 1.0 or 1.5 micrograms/kg/week) for one year with a follow-up period of six months. In addition, 303 patients received interferon alfa-2b (3 million International Units [MIU] three times a week as a comparator. This study showed that PegIntron was superior to interferon alfa-2b (**Table 7**).

In the PegIntron combination trial, 1,530 naïve patients were treated for one year with one of the following combination regimens:
- PegIntron (1.5 micrograms/kg/week) + ribavirin (800 mg/day), (n = 511).
- PegIntron (1.5 micrograms/kg/week for one month followed by 0.5 microgram/kg/week for 11 months) + ribavirin (1,000/1,200 mg/day), (n = 514).
- Interferon alfa-2b (3 MIU three times a week) + ribavirin (1,000/1,200 mg/day) (n = 505).

In this trial, the combination of PegIntron (1.5 micrograms/kg/week) and ribavirin was significantly more effective than the combination of interferon alfa-2b and ribavirin (**Table 7**), particularly in patients infected with Genotype 1 (**Table 8**). Sustained response was assessed by the response rate six months after the cessation of treatment.

HCV genotype and baseline virus load are prognostic factors which are known to affect response rates. However, response rates in this trial were shown to be dependent also on the dose of ribavirin administered in combination with PegIntron or interferon alfa-2b. In those patients that received > 10.6 mg/kg ribavirin (800 mg dose in typical 75 kg patient), regardless of genotype or viral load, response rates were significantly higher than in those patients that received ≤ 10.6 mg/kg ribavirin (**Table 8**), while response rates in patients that received > 13.2 mg/kg ribavirin were even higher.

Table 7 Sustained virological response (% patients HCV negative)

	PegIntron monotherapy				**PegIntron + ribavirin**		
Treatment regimen	**P 1.5**	**P 1.0**	**P 0.5**	**I**	**P 1.5/R**	**P 0.5/R**	**I/R**
Number of patients	304	297	315	303	511	514	505
Response at end of treatment	49 %	41 %	33 %	24 %	65 %	56 %	54 %

Sustained response	**23 %***	**25 %**	**18 %**	**12 %**	**54 %****	**47 %**	**47 %**

P 1.5 PegIntron 1.5 micrograms/kg
P 1.0 PegIntron 1.0 microgram/kg
P 0.5 PegIntron 0.5 microgram/kg
I Interferon alfa-2b 3 MIU
P 1.5/R PegIntron (1.5 micrograms/kg) + ribavirin (800 mg)
P 0.5/R PegIntron (1.5 to 0.5 microgram/kg) + ribavirin (1,000/1,200 mg)
I/R Interferon alfa-2b (3 MIU) + ribavirin (1,000/1,200 mg)
* $p < 0.001$ P 1.5 vs. I
** $p = 0.0143$ P 1.5/R vs. I/R

Table 8 Sustained response rates with PegIntron + ribavirin (by ribavirin dose , genotype and viral load)

HCV Genotype	**Rebetol dose (mg/kg)**	**P 1.5/R**	**P 0.5/R**	**I/R**
All Genotypes	**All**	**54 %**	**47 %**	**47 %**
	≤ 10.6	50 %	41 %	27 %
	> 10.6	61 %	48 %	47 %
Genotype 1	**All**	**42 %**	**34 %**	**33 %**
	≤ 10.6	38 %	25 %	20 %
	> 10.6	48 %	34 %	34 %
Genotype 1 ≤ 600,000 IU/ml	All	73 %	51 %	45 %
	≤ 10.6	74 %	25 %	33 %
	> 10.6	71 %	52 %	45 %
Genotype 1 > 600,000 IU/ml	All	30 %	27 %	29 %
	≤ 10.6	27 %	25 %	17 %
	> 10.6	37 %	27 %	29 %
Genotype 2/3	**All**	**82 %**	**80 %**	**79 %**
	≤ 10.6	79 %	73 %	50 %
	> 10.6	88 %	80 %	80 %

P 1.5/R PegIntron (1.5 micrograms/kg) + ribavirin (800 mg)
P 0.5/R PegIntron (1.5 to 0.5 microgram/kg) + ribavirin (1,000/1,200 mg)
I/R Interferon alfa-2b (3 MIU) + ribavirin (1,000/1,200 mg)

In the PegIntron monotherapy study, the Quality of Life was generally less affected by 0.5 microgram/kg of PegIntron than by either 1.0 microgram/kg of PegIntron once weekly or 3 MIU of interferon alfa-2b three times a week.

In a separate trial, 224 patients with genotype 2 or 3 received PegIntron, 1.5 microgram/kg subcutaneously, once weekly, in combination with ribavirin 800 mg –1,400 mg p.o. for 6 months (based on body weight, only three patients weighing > 105 kg, received the 1,400 mg dose, which has not yet been validated) (**Table 9**). Twenty-four % had bridging fibrosis or cirrhosis (Knodell 3/4).

Table 9. Virologic Response at End of Treatment, Sustained Virologic Response and Relapse by HCV Genotype and Viral Load*

	PegIntron 1.5 μg/kg Once Weekly Plus Rebetol 800-1400 mg/day		
	End of Treatment Response	Sustained Virologic Response	Relapse
All Subjects	94 % (211/224)	81 % (182/224)	12 % (27/224)
HCV 2	100 % (42/42)	93 % (39/42)	7 % (3/42)
≤ 600,000 IU/ml	100 % (20/20)	95 % (19/20)	5 % (1/20)
> 600,000	100 % (22/22)	91 % (20/22)	9 % (2/22)

IU/mL			
HCV 3	93 % (169/182)	79 % (143/182)	14 % (24/166)
≤ 600,000 IU/ml	93 % (92/99)	86 % (85/99)	8 % (7/91)
> 600,000 IU/ml	93 % (77/83)	70 % (58/83)	23 % (17/75)

* Any subject with an undetectable HCV-RNA level at the Follow-Up Week 12 visit and missing data at the Follow-Up Week 24 visit was considered a sustained responder. Any subject with missing data in and after the Follow-Up Week 12 window was considered to be a non-responder at Week 24 of follow-up.

The 6 month treatment duration in this trial was better tolerated than one year of treatment in the pivotal combination trial; for discontinuation 5 % vs. 14 %, for dose modification 18 % vs. 49 %.

Predictability of sustained virological response
Virological reponse by week 12, defined as a 2-log viral load decrease or undetectable levels of HCV RNA has been shown to be predictive for sustained response (**Table 10**).

Table 10 Predictability of sustained response by viral response at week 12 and genotype*

Treatment	Genotype	Viral response at week 12	Sustained response	Negative predictive value
PegIntron 1.5 + ribavirin (> 10.6 mg/kg) 48-week treatment	1	Yes 75 % (82/110)	71 % (58/82)	----
		No 25 % (28/110)	0 % (0/28)	100 %
PegIntron 1.5 + ribavirin 800-1,400 mg 24-week treatment	2 and 3	Yes 99 % (213/215)	83 % (177/213)	----
		No 1 % (2/215)	50 % (1/2)	50 %

* reflects patients with 12 week data available

The negative predictive value for sustained response in patients treated with PegIntron in monotherapy was 98 %.

5.2 Pharmacokinetic properties

PegIntron is a well characterized polyethylene glycol-modified ("pegylated") derivative of interferon alfa-2b and is predominantly composed of monopegylated species. The plasma half-life of PegIntron is prolonged compared with non-pegylated interferon alfa-2b. PegIntron has a potential to depegylate to free interferon alfa-2b. The biologic activity of the pegylated isomers is qualitatively similar, but weaker than free interferon alfa-2b.

Following subcutaneous administration, maximal serum concentrations occur between 15-44 hours post-dose, and are sustained for up to 48-72 hours post-dose.

PegIntron C_{max} and AUC measurements increase in a dose-related manner. Mean apparent volume of distribution is 0.99 l/kg.

Upon multiple dosing, there is an accumulation of immunoreactive interferons. There is, however, only a modest increase in biologic activity as measured by a bioassay.

Mean (SD) PegIntron elimination half-life is approximately 40 hours (13.3 hours), with apparent clearance of 22.0 ml/hr·kg. The mechanisms involved in clearance of interferons in man have not yet been

fully elucidated. However, renal elimination may account for a minority (approximately 30 %) of PegIntron apparent clearance.

Renal function: Renal clearance appears to account for 30 % of total clearance of PegIntron. In a single dose study (1.0 microgram/kg) in patients with impaired renal function, C_{max}, AUC, and half-life increased in relation to the degree of renal impairment.

Based on these data, no dose modification is recommended based on creatinine clearance. However, because of marked intra-subject variability in interferon pharmacokinetics, it is recommended that patients be monitored closely during treatment with PegIntron (see section **4.2**). Patients with severe renal dysfunction or creatinine clearance < 50 ml/min must not be treated with PegIntron.

Hepatic function: The pharmacokinetics of PegIntron have not been evaluated in patients with severe hepatic dysfunction.

Elderly patients ≥ 65 years of age: The pharmacokinetics of PegIntron following a single subcutaneous dose of 1.0 microgram/kg were not affected by age. The data suggest that no alteration in PegIntron dosage is necessary based on advancing age.

Patients under the age of 18 years: Specific pharmacokinetic evaluations have not been performed on these patients. PegIntron is indicated for the treatment of chronic hepatitis C only in patients 18 years of age or older.

Interferon neutralising factors: Interferon neutralising factor assays were performed on serum samples of patients who received PegIntron in the clinical trial. Interferon neutralising factors are antibodies which neutralise the antiviral activity of interferon. The clinical incidence of neutralising factors in patients who received PegIntron 0.5 micrograms/kg is 1.1 %.

5.3 Preclinical safety data

PegIntron: Adverse events not observed in clinical trials were not seen in toxicity studies in monkeys. These studies were limited to four weeks due to the appearance of anti-interferon antibodies in most monkeys.

Reproduction studies of PegIntron have not been performed. Interferon alfa-2b has been shown to be an abortifacient in primates. PegIntron is likely to also cause this effect. Effects on fertility have not been determined. PegIntron showed no genotoxic potential. (seesection **4.6** for relevant human data. It is not known whether the components of this medicinal product are excreted in human milk. Therefore, nursing must be discontinued prior to the initiation of therapy.)

The relative non-toxicity of monomethoxy-polyethylene glycol (mPEG), which is liberated from PegIntron by metabolism *in vivo* has been demonstrated in preclinical acute and subchronic toxicity studies in rodents and monkeys, standard embryo-foetal development studies and in *in vitro* mutagenicity assays.

PegIntron plus ribavirin: When used in combination with ribavirin, PegIntron did not cause any effects not previously seen with either active substance alone. The major treatment-related change was a reversible, mild to moderate anaemia, the severity of which was greater than that produced by either active substance alone.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder for solution for injection:

Disodium phosphate, anhydrous,

Sodium dihydrogen phosphate dihydrate,
Sucrose,
Polysorbate 80.
Solvent for parenteral use:
Water for injections.

6.2 Incompatibilities

This medicinal product should only be reconstituted with the solvent provided and must not be mixed with other medicinal products (see also section **6.6**).

6.3 Shelf life

3 years

After reconstitution:
- Chemical and physical in-use stability has been demonstrated for 24 hours at 2°C - 8ºC.
- From a microbiological point of view, the product is to be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C - 8°C.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).

6.5 Nature and contents of container

The powder is contained in a 2 ml vial, Type I flint glass, with a butyl rubber stopper in an aluminium flip-off seal with a polypropylene bonnet. The solvent is presented in a 2 ml ampoule, Type I flint glass. PegIntron 50 micrograms is supplied as:
- 1 vial of powder for solution for injection and 1 ampoule of solvent for parenteral use;
- 1 vial of powder for solution for injection, 1 ampoule of solvent for parenteral use, 1 injection syringe, 2 injection needles and 1 cleansing swab;
- 4 vials of powder for solution for injection and 4 ampoules of solvent for parenteral use;
- 4 vials of powder for solution for injection, 4 ampoules of solvent for parenteral use, 4 injection syringes, 8 injection needles and 4 cleansing swabs;
- 6 vials of powder for solution for injection and 6 ampoules of solvent for parenteral use.
- 12 vials of powder for solution for injection, 12 ampoules of solvent for parenteral use, 12 injection syringes, 24 injection needles and 12 cleansing swabs.

Not all pack sizes may be marketed

6.6 Instructions for use and handling, and disposal

PegIntron is supplied as a powder of peginterferon alfa-2b at a strength of 50 micrograms for single use. Each vial must be reconstituted with 0.7 ml of water for injections for administration of up to 0.5 ml of solution. A small volume is lost during preparation of PegIntron for injection when the dose is measured and injected. Therefore, each vial contains an excess amount of solvent and PegIntron powder to ensure delivery of the labelled dose in 0.5 ml of PegIntron, solution for injection. The reconstituted solution has a concentration of 50 micrograms/0.5 ml.

Using a sterilised injection syringe and injection needle, inject 0.7 ml of water for injections into the vial of PegIntron. Agitate gently to complete dissolution of powder. The appropriate dose can then be withdrawn with a sterilised injection syringe and injected.

As for all parenteral medicinal products, inspect visually the reconstituted solution prior to administration. The reconstituted solution should be clear and colourless. Do not use if discolouration or particulate

matter is present. Discard any unused material.

7. MARKETING AUTHORISATION HOLDER

SP Europe
73, rue de Stalle
B-1180 Bruxelles
Belgium

8. MARKETING AUTHORISATION NUMBERS

EU/1/00/131/001
EU/1/00/131/002
EU/1/00/131/003
EU/1/00/131/004
EU/1/00/131/005
EU/1/00/131/026

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

25 May 2000

10. DATE OF REVISION OF THE TEXT

1. NAME OF THE MEDICINAL PRODUCT

PegIntron 80 micrograms powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of PegIntron, powder for solution for injection contains 80 micrograms of peginterferon alfa-2b as measured on a protein basis.
Each vial provides 80 micrograms/0.5 ml of peginterferon alfa-2b when reconstituted as recommended.

The active substance is a covalent conjugate of recombinant interferon alfa-2b* with monomethoxy polyethylene glycol. The potency of this product should not be compared to that of another pegylated or non-pegylated protein of the same therapeutic class. For more information, see section **5.1.**
*produced by rDNA technology in *E.coli* cells harbouring a genetically engineered plasmid hybrid encompassing an interferon alfa-2b gene from human leukocytes

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection
The white powder is contained in a 2 ml glass vial and the clear and colourless solvent is presented in a 2 ml glass ampoule.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PegIntron is indicated for the treatment of adult patients with chronic hepatitis C who have elevated transaminases without liver decompensation and who are positive for serum HCV-RNA or anti-HCV (see section **4.4**).

The best way to use PegIntron in this indication is in combination with ribavirin.

This combination is indicated in naïve patients as well as in patients who have previously responded (with normalisation of ALT at the end of treatment) to interferon alpha monotherapy but who have subsequently relapsed.

Interferon monotherapy, including PegIntron, is indicated mainly in case of intolerance or contraindication to ribavirin.

Please refer also to the ribavirin Summary of Product Characteristics (SPC) when PegIntron is to be used in combination with ribavirin.

4.2 Posology and method of administration

Treatment should be initiated and monitored only by a physician experienced in the management of patients with hepatitis C.

Dose to be administered
PegIntron should be administered as a once weekly subcutaneous injection. The dose administered depends on whether it is used in combination with ribavirin or as monotherapy.

Combination therapy
PegIntron 1.5 micrograms/kg/week in combination with ribavirin capsules.

The intended dose of 1.5 μg/kg of PegIntron to be used in combination with ribavirin may be delivered in weight categories with the pen/vial strengths according to **Table 1**. Ribavirin capsules are to be administered orally each day in two divided doses with food (morning and evening).

Table 1 - Dosing for Combination Therapy

Body Weight (kg)	PegIntron		Ribavirin Capsules	
	Vial/Pen Strength (μg/0.5ml)	Administer Once Weekly (ml)	Total Daily Dose (mg)	Number of Capsules (200 mg)
< 40	50	0.5	800	4[a]
40-50	80	0.4	800	4[a]
51-64	80	0.5	800	4[a]
65-75	100	0.5	1,000	5[b]
76-85	120	0.5	1,000	5[b]
> 85	150	0.5	1,200	6[c]

a: 2 morning, 2 evening
b: 2 morning, 3 evening
c: 3 morning, 3 evening

Duration of treatment
Predictability of sustained virological response: Patients infected with virus genotype 1 who fail to achieve virological response at Week 12 are highly unlikely to become sustained virological responders (see also section **5.1**).

- **Genotype 1**: For patients who exhibit virological response at week 12, treatment should be continued for another nine month period (i.e., a total of 48 weeks).
- **Genotypes 2 or 3**: It is recommended that all patients be treated for 24 weeks.
- **Genotype 4:** In general, patients infected with genotype 4 are considered harder to treat and limited study data (n=66) indicate they are compatible with a posology as for genotype 1.

PegIntron monotherapy
As monotherapy the PegIntron regimen is 0.5 or 1.0 microgram/kg/week. The lowest vial or pen strength available is 50 μg/0.5 ml; therefore for patients prescribed 0.5 μg/kg/week, doses must be adjusted by volume as shown in **Table 2**. For the 1.0 μg/kg dose, similar volume adjustments can be made or alternate vial strengths can be used as shown in **Table 2**.

Table 2- Monotherapy Dosing

	0.5 μg/kg		1.0 μg/kg	
Body Weight (kg)	Vial/Pen Strength (μg/0.5ml)	Administer Once Weekly (ml)	Vial/Pen Strength (μg/0.5ml)	Administer Once Weekly (ml)
30-35	50*	0.15	50	0.3
36-45	50*	0.2	50	0.4
46-56	50*	0.25	50	0.5
57-72	50	0.3	80	0.4
73-88	50	0.4	80	0.5

89-106	50	0.5	100	0.5
> 106**	80	0.4	120	0.5
* Must use vial. Minimum delivery for pen is 0.3 ml. ** For patients > 120 kg, use 80 µg/0.5 ml vial				

Duration of treatment
For patients who exhibit virological response at Week 12, treatment should be continued for at least another three-month period (i.e., a total of six months). The decision to extend therapy to one year of treatment should be based on prognostic factors (e.g., genotype, age > 40 years, male gender, bridging fibrosis).

Dose modification for all patients
If severe adverse reactions or laboratory abnormalities develop during treatment with PegIntron monotherapy or PegIntron in combination with ribavirin, modify the dosages of each product as appropriate, until the adverse reactions abate. Guidelines were developed in clinical trials for dose modification.

Combination Therapy Dose Reduction Guidelines

Table 2a Dose modification guidelines for combination therapy (with ribavirin)

Laboratory values	**Reduce only ribavirin dose to 600 mg/day* if:**	**Reduce only PegIntron dose to one-half dose if:**	**Discontinue combination therapy if:**
Haemoglobin	< 10 g/dl	-	< 8.5 g/dl
Haemoglobin in: Patients with history of stable cardiac disease	≥ 2 g/dl decrease in haemoglobin during any four week period during treatment (permanent dose reduction)		< 12 g/dl after four weeks of dose reduction
White blood cells	-	< 1.5 x 10^9/l	< 1.0 x 10^9/l
Neutrophils	-	< 0.75 x 10^9/l	< 0.5 x 10^9/l
Platelets	-	< 50 x 10^9/l	< 25 x 10^9/l
Bilirubin – direct	-	-	2.5 x ULN**
Bilirubin - indirect	> 5 mg/dl	-	> 4 mg/dl (for > 4 weeks)
Creatinine	-	-	> 2.0 mg/dl
ALT/AST	-	-	2 x baseline and > 10 x ULN**

* Patients whose dose of ribavirin is reduced to 600 mg daily receive one 200 mg capsule in the morning and two 200 mg capsules in the evening.

** Upper limit of normal

Dose reduction of PegIntron may be accomplished by either reducing the prescribed volume by one-half or by utilizing a lower dose strength as shown in **Table 2b**.

Table 2b – Reduced PegIntron Dosing for Combination Therapy

Body Weight (kg)	**Target Reduced Dose (µg)**	**Vial/Pen Strength (µg/0.5 ml)**	**Administer Once Weekly (ml)**	**Amount Delivered (µg)**
< 40	25	50*	0.25	25
40-50	32	50	0.3	30
51-64	40	50	0.4	40
65-75	50	50	0.5	50

76-85	60	80	0.4	64
> 85	75	100	0.4	80
*Must use vial. Minimum delivery for pen is 0.3 ml.				

PegIntron Monotherapy Dose Reduction Guidelines

Dose modification guidelines for patients who use PegIntron monotherapy are shown in **Table 3a.**

Table 3a Dose modification guidelines for PegIntron monotherapy		
Laboratory values	**Reduce PegIntron to one-half dose if:**	**Discontinue PegIntron if:**
Neutrophils	< 0.75 x 10^9/l	< 0.5 x 10^9/l
Platelets	< 50 x 10^9/l	< 25 x 10^9/l

Dose reduction for patients who use 0.5 µg/kg PegIntron monotherapy must be accomplished by reducing the prescribed volume by one-half. The 50 µg/0.5 ml vial must be used if necessary since the pen can only deliver a minimum volume of 0.3 ml.

For patients who use 1.0 µg/kg PegIntron monotherapy, dose reduction may be accomplished by reducing the prescribed volume by one-half or by utilizing a lower dose strength as shown in **Table 3b**.

Table 3b – Reduced PegIntron Dose for the 1.0 µg/kg Monotherapy Regimen				
Body Weight (kg)	**Target Reduced Dose (µg)**	**Vial/Pen Strength (µg/0.5ml)**	**Administer Once Weekly (ml)**	**Amount Delivered (µg)**
30-35	15	50*	0.15	15
36-45	20	50*	0.20	20
46-56	25	50*	0.25	25
57-72	32	50	0.3	30
73-89	40	50	0.4	40
90-106	50	50	0.5	50
> 106	60	80	0.4	64
*Must use vial. Minimum delivery for pen is 0.3 ml.				

Special populations

Use in renal impairment: The clearance of PegIntron is reduced in patients with significant renal impairment. Patients with creatinine clearance ≤ 50 ml/minute must not be treated with PegIntron (see section **5.2**). It is recommended that patients with moderate renal impairment be closely monitored and that their weekly dose of PegIntron be reduced if medically appropriate.

Use in hepatic impairment: The safety and efficacy of PegIntron therapy has not been evaluated in patients with severe hepatic dysfunction, therefore PegIntron must not be used for these patients.

Use in the elderly (≥ 65 years of age): There are no apparent age-related effects on the pharmacokinetics of PegIntron. Data from elderly patients treated with a single dose of PegIntron suggest no alteration in PegIntron dose is necessary based on age (see section **5.2**).

Use in patients under the age of 18 years: PegIntron is not recommended for use in children or adolescents under the age of 18, as there is no experience in this group.

4.3 Contraindications

- Hypersensitivity to the active substance or to any interferon or to any of the excipients;
- Pregnant women;
- Women who are breast-feeding;
- A history of severe pre-existing cardiac disease, including unstable or uncontrolled cardiac disease in the previous six months (see section **4.4**);
- Severe, debilitating medical conditions, including patients with chronic renal failure or creatinine clearance < 50 ml/minute;
- Autoimmune hepatitis or a history of autoimmune disease;
- Severe hepatic dysfunction or decompensated cirrhosis of the liver;
- Pre-existing thyroid disease unless it can be controlled with conventional treatment;
- Epilepsy and/or compromised central nervous system (CNS) function.

4.4 Special warnings and special precautions for use

There is no experience with PegIntron in combination with ribavirin in patients who have relapsed after interferon alpha + ribavirin therapy.

All patients in the chronic hepatitis C studies had a liver biopsy before inclusion, but in certain cases (i.e. patients with genotype 2 and 3), treatment may be possible without histological confirmation. Current treatment guidelines should be consulted as to whether a liver biopsy is needed prior to commencing treatment.

Acute hypersensitivity: Acute hypersensitivity reactions (e.g., urticaria, angioedema, bronchoconstriction, anaphylaxis) have been observed rarely during interferon alfa-2b therapy. If such a reaction develops during treatment with PegIntron, discontinue treatment and institute appropriate medical therapy immediately. Transient rashes do not necessitate interruption of treatment.

Cardiovascular system: As with interferon alfa-2b, patients with a history of congestive heart failure, myocardial infarction and/or previous or current arrhythmic disorders, receiving PegIntron therapy require close monitoring. It is recommended that patients who have pre-existing cardiac abnormalities have electrocardiograms taken prior to and during the course of treatment. Cardiac arrhythmias (primarily supraventricular) usually respond to conventional therapy but may require discontinuation of PegIntron therapy.

Psychiatric and Central Nervous System (CNS): If treatment with peginterferon alfa-2b is judged necessary in patients with existence or history of severe psychiatric conditions, this should only be initiated after having ensured appropriate individualised diagnostic and therapeutic management of the psychiatric condition.
Severe CNS effects, particularly depression, suicidal ideation and attempted suicide have been observed in some patients during PegIntron therapy. Other CNS effects including aggressive behaviour, confusion and alterations of mental status have been observed with alpha interferon. If patients develop psychiatric or CNS problems, including clinical depression, it is recommended that the patient be carefully monitored due to the potential seriousness of these undesirable effects. If symptoms persist or worsen, discontinue PegIntron therapy.
More significant obtundation and coma, including cases of encephalopathy, have been observed in some patients, usually elderly, treated at higher doses for oncology indications. While these effects are generally reversible, in a few patients full resolution took up to three weeks. Very rarely, seizures have occurred with high doses of interferon alpha.

Liver function: As with all interferons, discontinue treatment with PegIntron in patients who develop prolongation of coagulation markers which might indicate liver decompensation.

Fever: While fever may be associated with the flu-like syndrome reported commonly during interferon therapy, other causes of persistent fever must be ruled out.

Hydration: Adequate hydration must be maintained in patients undergoing PegIntron therapy since hypotension related to fluid depletion has been seen in some patients treated with alpha interferons. Fluid replacement may be necessary.

Pulmonary changes: Pulmonary infiltrates, pneumonitis, and pneumonia, occasionally resulting in fatality, have been observed rarely in interferon alpha treated patients. Any patient developing fever, cough, dyspnea or other respiratory symptoms must have a chest X-ray taken. If the chest X-ray shows pulmonary infiltrates or there is evidence of pulmonary function impairment, the patient is to be monitored closely, and, if appropriate, discontinue interferon alpha. Prompt discontinuation of interferon alpha administration and treatment with corticosteroids appear to be associated with resolution of pulmonary adverse events.

Autoimmune disease: The development of auto-antibodies and autoimmune disorders has been reported during treatment with alpha interferons. Patients predisposed to the development of autoimmune disorders may be at increased risk. Patients with signs or symptoms compatible with autoimmune disorders should be evaluated carefully, and the benefit-risk of continued interferon therapy should be reassessed (see also section **4.4 Thyroid changes** and **4.8**).

Ocular changes: Ophthalmologic disorders, including retinal haemorrhages, cotton wool spots, and retinal artery or vein obstruction have been reported in rare instances after treatment with alpha interferons (see section **4.8**). All patients should have a baseline eye examination. Any patient complaining of ocular symptoms, including loss of visual acuity or visual field must have a prompt and complete eye examination. Periodic visual examinations are recommended during PegIntron therapy, particularly in patients with disorders that may be associated with retinopathy, such as diabetes mellitus or hypertension. Discontinuation of PegIntron should be considered in patients who develop new or worsening ophthalmological disorders.

Thyroid changes: Infrequently, patients treated for chronic hepatitis C with interferon alpha have developed thyroid abnormalities, either hypothyroidism or hyperthyroidism. Determine thyroid stimulating hormone (TSH) levels if, during the course of therapy, a patient develops symptoms consistent with possible thyroid dysfunction. In the presence of thyroid dysfunction, PegIntron treatment may be continued if TSH levels can be maintained in the normal range by medication.

Metabolic disturbances: Hypertriglyceridemia and aggravation of hypertriglyceridemia, sometimes severe, have been observed. Monitoring of lipid levels is, therefore, recommended.

HCV/HIV Coinfection
Patients co-infected with HIV and receiving Highly Active Anti-Retroviral Therapy (HAART) may be at increased risk of developing lactic acidosis. Caution should be used when adding PegIntron and ribavirin to HAART therapy (see ribavirin SPC).
Co-infected patients with advanced cirrhosis receiving HAART may be at increased risk of hepatic decompensation and death. Adding treatment with alfa interferons alone or in combination with ribavirin may increase the risk in this patient subset.

Organ transplant recipients: The safety and efficacy of PegIntron alone or in combination with ribavirin for the treatment of hepatitis C in liver or other organ transplant recipients have not been studied. Preliminary data indicates that interferon alpha therapy may be associated with an increased rate of kidney graft rejection. Liver graft rejection has also been reported.

Other: Due to reports of interferon alpha exacerbating pre-existing psoriatic disease and sarcoidosis, use of PegIntron in patients with psoriasis or sarcoidosis is recommended only if the potential benefit justifies the potential risk.

Laboratory tests: Standard haematologic tests, blood chemistry and a test of thyroid function must be conducted in all patients prior to initiating therapy. Acceptable baseline values that may be considered as a guideline prior to initiation of PegIntron therapy are:

- Platelets ≥ 100,000/mm^3
- Neutrophil count ≥ 1,500/mm^3
- TSH level must be within normal limits

Laboratory evaluations are to be conducted at weeks 2 and 4 of therapy, and periodically thereafter as clinically appropriate.

4.5 Interaction with other medicinal products and other forms of interaction

Results of a single-dose study with PegIntron demonstrated no effect on the activity of cytochrome (CY) P1A2, CYP2C8/9, CYP2D6, and hepatic CYP3A4 or N-acetyl transferase. Caution should be advised in the interpretation of these results as the use of other forms of interferon alpha result in a 50 % reduction in the clearance and thus a doubling of plasma concentrations of theophylline, a substrate of CYP1A2.

No pharmacokinetic interactions were noted between PegIntron and ribavirin in a multiple-dose pharmacokinetic study.

4.6 Pregnancy and lactation

There are no adequate data on the use of interferon alfa-2b in pregnant women. Interferon alfa-2b has been shown to be abortifacient in primates. PegIntron is likely to also cause this effect. PegIntron should not be used during pregnancy (see section **5.3**).

PegIntron is recommended for use in fertile women only when they are using effective contraception during the treatment period.

Lactation: It is not known whether the components of this medicinal product are excreted in human milk. Because of the potential for adverse reactions in nursing infants, nursing must be discontinued prior to initiation of treatment.

Ribavirin is teratogenic and embryocidal and must not be used in pregnant women (see ribavirin SPC, **5.3**).

4.7 Effects on ability to drive and use machines

Patients who develop fatigue, somnolence or confusion during treatment with PegIntron are cautioned to avoid driving or operating machinery.

4.8 Undesirable effects

The safety of PegIntron is evaluated from data from two clinical trials: one with PegIntron monotherapy, one with PegIntron in combination with ribavirin. In both cases, patients were treated for one year.

Table 4 describes the regimens and patient exposure for one year of treatment in patients with no previous exposure to interferon (interferon-naïve patients). Because of a significant overlap in the pattern of undesirable effects with PegIntron monotherapy, groups of patients have been brought together in **Table 5** to show the pattern of reported effects for all monotherapy groups.

Table 4	Regimens and patient exposure	
Treatment	**Regimen**	**Number of patients treated for one year**
PegIntron + ribavirin	PegIntron (1.5 micrograms/kg/week) + ribavirin (> 10.6 mg/kg/day)	188
Interferon alfa-2b + ribavirin	Interferon alfa-2b (3 MIU three times a week) + ribavirin (1,000/1,200 mg/day)	505
PegIntron monotherapy	PegIntron (0.5 microgram/kg/week)	315
	PegIntron (1.0 microgram/kg/week)	297
	PegIntron (1.5 micrograms/kg/week)	304

Table 5 Undesirable effects reported in clinical trials (≥ 10 % of patients in PegIntron + ribavirin group)			
	PegIntron + ribavirin	**Interferon alfa-2b + ribavirin**	**PegIntron monotherapy**
Application site disorder			
Injection site inflammation	20 %	17 %	39-44 %
Injection site reaction	54 %	36 %	7-9 %
Body as a whole			
Headache	58 %	57 %	57-63 %
Fatigue	56 %	59 %	43 %
Rigors	42 %	40 %	33-43 %
Fever	39 %	32 %	29-43 %
Flu-like symptoms	21 %	23 %	18-25 %
Asthenia	28 %	17 %	12-14 %
Weight decrease	30 %	19 %	8-18 %
Gastrointestinal			
Nausea	43 %	31 %	20-23 %
Anorexia	35 %	26 %	10-25 %
Diarrhoea	20 %	13 %	14-17 %
Abdominal pain	12 %	9 %	11 %
Vomiting	16 %	10 %	4-7 %
Musculoskeletal			
Myalgia	49 %	49 %	46-60 %
Arthralgia	31 %	26 %	23-28 %
Musculoskeletal pain	15 %	11 %	11-13 %
Psychiatric			
Depression	34 %	32 %	26 %
Irritability	32 %	34 %	19 %
Insomnia	37 %	41 %	16-19 %
Anxiety	14 %	14 %	8 %
Concentration impaired	18 %	21 %	9-10 %
Emotional lability	11 %	10 %	5 %
Respiratory system			
Pharyngitis	10 %	7 %	3 %
Coughing	14 %	11 %	4 %
Dyspnea	26 %	22 %	5 %
Skin and appendages			
Alopecia	45 %	32 %	20-34 %
Pruritus	27 %	27 %	7-9 %
Skin dry	23 %	21 %	6-9 %
Rash	21 %	21 %	5-7 %
Other			
Dizziness	17 %	16 %	7-12 %
Infection viral	10 %	5 %	4-5 %
Mouth dry	10 %	8 %	4-8 %

Table 6 Undesirable effects reported in clinical trials (1%-< 10% of patients treated with PegIntron + ribavirin or PegIntron monotherapy)		
Body system	**5-10%**	**1-<5%**
Body as a whole	chest pain, RUQ pain, malaise	erythema, injection site pain, flushing, thirst, herpes simplex, face or peripheral oedema, dehydration
Cardiovascular		tachycardia, palpitation, hypotension, hypertension, syncope
Central/peripheral nervous system	paresthesia	hypoaesthesia, hyperaesthesia, hypertonia, decreased libido, confusion, tremor, vertigo, migraine, tinnitus, hearing impairment/loss, ataxia, neuralgia
Endocrine	hypothyroidism,	hyperthyroidism, amenorrhoea, prostatitis, hyperuricemia, hypocalcemia
Gastrointestinal	dyspepsia,	constipation, taste perversion, loose stools, stomatitis, ulcerative stomatitis, gingival bleeding, glossitis, flatulence, hemorrhoids, gastroesophageal reflux, hepatomegaly, bilirubinemia, gingivitis
Haematologic	anaemia, leukopaenia	thrombocytopenia, lymphadenopathy,
Musculoskeletal		arthritis
Ocular		blurred vision, conjunctivitis, lacrimal gland disorder, eye pain
Psychiatric	agitation, nervousness	aggressive behaviour, somnolence, behavior disorder, apathy, appetite increased, sleep disorder, dreaming abnormal
Reproductive	menstrual disorder, menorrhagia	ovarian disorder, vaginal disorder, sexual dysfunction (not specified), impotence, breast pain
Respiratory		nonproductive cough, rhinitis, sinusitis, bronchitis, respiratory disorder, nasal congestion, rhinorrhea, dysphonia, epistaxis
Resistance mechanism		otitis media, fungal infection, bacterial infection
Skin and appendages	increased sweating	erythematous rash, eczema, photosensitivity reaction, maculopapular rash, abnormal hair texture, acne, dermatitis, furunculosis, nail disorder, psoriasis, urticaria
Urinary		micturition frequency, urine abnormal

Most cases of neutropaenia and thrombocytopaenia were mild (WHO grades 1 or 2). There were some cases of more severe neutropenia in patients treated with the recommended doses of PegIntron in combination with ribavirin (WHO grade 3: 39 of 186 [21 %]; and WHO grade 4: 13 of 186 [7 %]).

In a clinical trial, approximately 1.2 % of patients treated with PegIntron or interferon alfa-2b in combination with ribavirin reported life-threatening psychiatric events during treatment. These events included suicidal ideation and attempted suicide (see section **4.4)**. Following marketing, psychosis and hallucination have been reported rarely.

Rarely reported events with interferon alfa-2b, including PegIntron, include seizure, pancreatitis, arrhythmia, peripheral neuropathy, diabetes, rhabdomyolysis, myositis, renal insufficiency and renal failure.

Cardiovascular (CVS) adverse events, particularly arrhythmia, appeared to be correlated mostly with pre-existing CVS disease and prior therapy with cardiotoxic agents (see section **4.4**). Cardiomyopathy, that may be reversible upon discontinuation of interferon alpha, has been reported rarely in patients without prior evidence of cardiac disease.

Very rarely cases of erythema multiforme, Stevens Johnson syndrome, toxic epidermal necrolysis, cardiac ischaemia, myocardial infarction, cerebrovascular ischaemia, cerebrovascular hemorrhage, encephalopathy, sarcoidosis or exacerbation of sarcoidosis, interstitial lung disease and injection site necrosis have been reported. Ulcerative and ischaemic colitis have been reported very rarely with PegIntron.

Very rarely, interferon alfa-2b or PegIntron used alone or in combination with ribavirin may be associated with aplastic anaemia.

Ophthalmological disorders that have been reported rarely with alpha interferons include retinopathies (including macular oedema), retinal haemorrhages, retinal artery or vein obstruction, cotton wool spots, loss of visual acuity or visual field, optic neuritis, and papilloedema (see section **4.4**).

A wide variety of autoimmune and immune-mediated disorders have been reported with alpha interferons including thyroid disorders, idiopathic and thrombotic thrombocytopenic purpura, vasculitis, neuropathies including mononeuropathies (see also section **4.4**, **Autoimmune disorders**).

4.9 Overdose

In clinical trials, cases of accidental overdose, at never more than twice the prescribed dose, were reported. There were no serious reactions. Undesirable effects resolved during continued administration of PegIntron.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunostimulants, Cytokines and immunomodulators, Interferons, Peginterferon alfa-2b, ATC code: L03A B10.

Recombinant interferon alfa-2b is covalently conjugated with monomethoxy polyethylene glycol at an average degree of substitution of 1 mole of polymer/mole of protein. The average molecular mass is approximately 31,300 daltons of which the protein moiety constitutes approximately 19,300.

Interferon alfa-2b
In vitro and *in vivo* studies suggest that the biological activity of PegIntron is derived from its interferon alfa-2b moiety.

Interferons exert their cellular activities by binding to specific membrane receptors on the cell surface. Studies with other interferons have demonstrated species specificity. However, certain monkey species, e.g., Rhesus monkeys, are susceptible to pharmacodynamic stimulation upon exposure to human type 1 interferons.

Once bound to the cell membrane, interferon initiates a complex sequence of intracellular events that include the induction of certain enzymes. It is thought that this process, at least in part, is responsible for the various cellular responses to interferon, including inhibition of virus replication in virus-infected cells, suppression of cell proliferation and such immunomodulating activities as enhancement

of the phagocytic activity of macrophages and augmentation of the specific cytotoxicity of lymphocytes for target cells. Any or all of these activities may contribute to interferon's therapeutic effects.

Recombinant interferon alfa-2b also inhibits viral replication *in vitro* and *in vivo*. Although the exact antiviral mode of action of recombinant interferon alfa-2b is unknown, it appears to alter the host cell metabolism. This action inhibits viral replication or if replication occurs, the progeny virions are unable to leave the cell.

PegIntron
PegIntron pharmacodynamics were assessed in a rising single-dose trial in healthy subjects by examining changes in oral temperature, concentrations of effector proteins such as serum neopterin and 2'5'-oligoadenylate synthetase (2'5'-OAS), as well as white cell and neutrophil counts. Subjects treated with PegIntron showed mild dose-related elevations in body temperature. Following single doses of PegIntron between 0.25 and 2.0 micrograms/kg/week, serum neopterin concentration was increased in a dose-related manner. Neutrophil and white cell count reductions at the end of week 4 correlated with the dose of PegIntron.

PegIntron clinical trials
Two pivotal trials have been conducted, one (C/I97-010) with PegIntron monotherapy; the other (C/I98-580) with PegIntron in combination with ribavirin. Eligible patients for these trials had chronic hepatitis C confirmed by a positive HCV-RNA polymerase chain reaction (PCR) assay (> 30 IU/ml), a liver biopsy consistent with a histological diagnosis of chronic hepatitis with no other cause for the chronic hepatitis, and abnormal serum ALT.

In the PegIntron monotherapy trial, a total of 916 naïve chronic hepatitis C patients were treated with PegIntron (0.5, 1.0 or 1.5 micrograms/kg/week) for one year with a follow-up period of six months. In addition, 303 patients received interferon alfa-2b (3 million International Units [MIU] three times a week as a comparator. This study showed that PegIntron was superior to interferon alfa-2b (**Table 7**).

In the PegIntron combination trial, 1,530 naïve patients were treated for one year with one of the following combination regimens:
- PegIntron (1.5 micrograms/kg/week) + ribavirin (800 mg/day), (n = 511).
- PegIntron (1.5 micrograms/kg/week for one month followed by 0.5 microgram/kg/week for 11 months) + ribavirin (1,000/1,200 mg/day), (n = 514).
- Interferon alfa-2b (3 MIU three times a week) + ribavirin (1,000/1,200 mg/day) (n = 505).

In this trial, the combination of PegIntron (1.5 micrograms/kg/week) and ribavirin was significantly more effective than the combination of interferon alfa-2b and ribavirin (**Table 7**), particularly in patients infected with Genotype 1 (**Table 8**). Sustained response was assessed by the response rate six months after the cessation of treatment.

HCV genotype and baseline virus load are prognostic factors which are known to affect response rates. However, response rates in this trial were shown to be dependent also on the dose of ribavirin administered in combination with PegIntron or interferon alfa-2b. In those patients that received > 10.6 mg/kg ribavirin (800 mg dose in typical 75 kg patient), regardless of genotype or viral load, response rates were significantly higher than in those patients that received ≤ 10.6 mg/kg ribavirin (**Table 8**), while response rates in patients that received > 13.2 mg/kg ribavirin were even higher.

Table 7 Sustained virological response (% patients HCV negative)

	PegIntron monotherapy				**PegIntron + ribavirin**		
Treatment regimen	**P 1.5**	**P 1.0**	**P 0.5**	**I**	**P 1.5/R**	**P 0.5/R**	**I/R**
Number of patients	304	297	315	303	511	514	505
Response at end of treatment	49 %	41 %	33 %	24 %	65 %	56 %	54 %

Sustained response	**23 %***	**25 %**	**18 %**	**12 %**	**54 %****	**47 %**	**47 %**

P 1.5 PegIntron 1.5 micrograms/kg
P 1.0 PegIntron 1.0 microgram/kg
P 0.5 PegIntron 0.5 microgram/kg
I Interferon alfa-2b 3 MIU
P 1.5/R PegIntron (1.5 micrograms/kg) + ribavirin (800 mg)
P 0.5/R PegIntron (1.5 to 0.5 microgram/kg) + ribavirin (1,000/1,200 mg)
I/R Interferon alfa-2b (3 MIU) + ribavirin (1,000/1,200 mg)
* $p < 0.001$ P 1.5 vs. I
** $p = 0.0143$ P 1.5/R vs. I/R

Table 8 Sustained response rates with PegIntron + ribavirin (by ribavirin dose , genotype and viral load)

HCV Genotype	**Rebetol dose (mg/kg)**	**P 1.5/R**	**P 0.5/R**	**I/R**
All Genotypes	**All**	**54 %**	**47 %**	**47 %**
	≤ 10.6	50 %	41 %	27 %
	> 10.6	61 %	48 %	47 %
Genotype 1	**All**	**42 %**	**34 %**	**33 %**
	≤ 10.6	38 %	25 %	20 %
	> 10.6	48 %	34 %	34 %
Genotype 1 ≤ 600,000 IU/ml	All	73 %	51 %	45 %
	≤ 10.6	74 %	25 %	33 %
	> 10.6	71 %	52 %	45 %
Genotype 1 > 600,000 IU/ml	All	30 %	27 %	29 %
	≤ 10.6	27 %	25 %	17 %
	> 10.6	37 %	27 %	29 %
Genotype 2/3	**All**	**82 %**	**80 %**	**79 %**
	≤ 10.6	79 %	73 %	50 %
	> 10.6	88 %	80 %	80 %

P 1.5/R PegIntron (1.5 micrograms/kg) + ribavirin (800 mg)
P 0.5/R PegIntron (1.5 to 0.5 microgram/kg) + ribavirin (1,000/1,200 mg)
I/R Interferon alfa-2b (3 MIU) + ribavirin (1,000/1,200 mg)

In the PegIntron monotherapy study, the Quality of Life was generally less affected by 0.5 microgram/kg of PegIntron than by either 1.0 microgram/kg of PegIntron once weekly or 3 MIU of interferon alfa-2b three times a week.

In a separate trial, 224 patients with genotype 2 or 3 received PegIntron, 1.5 microgram/kg subcutaneously, once weekly, in combination with ribavirin 800 mg –1,400 mg p.o. for 6 months (based on body weight, only three patients weighing > 105 kg, received the 1,400 mg dose, which has not yet been validated) (**Table 9**). Twenty-four % had bridging fibrosis or cirrhosis (Knodell 3/4).

Table 9. Virologic Response at End of Treatment, Sustained Virologic Response and Relapse by HCV Genotype and Viral Load*

	PegIntron 1.5 μg/kg Once Weekly Plus Rebetol 800-1400 mg/day		
	End of Treatment Response	Sustained Virologic Response	Relapse
All Subjects	94 % (211/224)	81 % (182/224)	12 % (27/224)
HCV 2	100 % (42/42)	93 % (39/42)	7 % (3/42)
≤ 600,000 IU/ml	100 % (20/20)	95 % (19/20)	5 % (1/20)
> 600,000	100 % (22/22)	91 % (20/22)	9 % (2/22)

IU/mL			
HCV 3	93 % (169/182)	79 % (143/182)	14 % (24/166)
≤ 600,000 IU/ml	93 % (92/99)	86 % (85/99)	8 % (7/91)
> 600,000 IU/ml	93 % (77/83)	70 % (58/83)	23 % (17/75)

* Any subject with an undetectable HCV-RNA level at the Follow-Up Week 12 visit and missing data at the Follow-Up Week 24 visit was considered a sustained responder. Any subject with missing data in and after the Follow-Up Week 12 window was considered to be a non-responder at Week 24 of follow-up.

The 6 month treatment duration in this trial was better tolerated than one year of treatment in the pivotal combination trial; for discontinuation 5 % vs. 14 %, for dose modification 18 % vs. 49 %.

Predictability of sustained virological response
Virological reponse by week 12, defined as a 2-log viral load decrease or undetectable levels of HCV RNA has been shown to be predictive for sustained response (**Table 10**).

Table 10 Predictability of sustained response by viral response at week 12 and genotype*

Treatment	Genotype	Viral response at week 12	Sustained response	Negative predictive value
PegIntron 1.5 + ribavirin (> 10.6 mg/kg) 48-week treatment	1	Yes 75 % (82/110)	71 % (58/82)	----
		No 25 % (28/110)	0 % (0/28)	100 %
PegIntron 1.5 + ribavirin 800-1,400 mg 24-week treatment	2 and 3	Yes 99 % (213/215)	83 % (177/213)	----
		No 1 % (2/215)	50 % (1/2)	50 %

* reflects patients with 12 week data available

The negative predictive value for sustained response in patients treated with PegIntron in monotherapy was 98 %.

5.2 Pharmacokinetic properties

PegIntron is a well characterized polyethylene glycol-modified (“pegylated”) derivative of interferon alfa-2b and is predominantly composed of monopegylated species. The plasma half-life of PegIntron is prolonged compared with non-pegylated interferon alfa-2b. PegIntron has a potential to depegylate to free interferon alfa-2b. The biologic activity of the pegylated isomers is qualitatively similar, but weaker than free interferon alfa-2b.

Following subcutaneous administration, maximal serum concentrations occur between 15-44 hours post-dose, and are sustained for up to 48-72 hours post-dose.

PegIntron C_{max} and AUC measurements increase in a dose-related manner. Mean apparent volume of distribution is 0.99 l/kg.

Upon multiple dosing, there is an accumulation of immunoreactive interferons. There is, however, only a modest increase in biologic activity as measured by a bioassay.

Mean (SD) PegIntron elimination half-life is approximately 40 hours (13.3 hours), with apparent clearance of 22.0 ml/hr·kg. The mechanisms involved in clearance of interferons in man have not yet been fully elucidated. However, renal elimination may account for a minority (approximately 30 %) of PegIntron apparent clearance.

Renal function: Renal clearance appears to account for 30 % of total clearance of PegIntron. In a single dose study (1.0 microgram/kg) in patients with impaired renal function, C_{max}, AUC, and half-life increased in relation to the degree of renal impairment.

Based on these data, no dose modification is recommended based on creatinine clearance. However, because of marked intra-subject variability in interferon pharmacokinetics, it is recommended that patients be monitored closely during treatment with PegIntron (see section **4.2**). Patients with severe renal dysfunction or creatinine clearance < 50 ml/min must not be treated with PegIntron.

Hepatic function: The pharmacokinetics of PegIntron have not been evaluated in patients with severe hepatic dysfunction.

Elderly patients ≥ 65 years of age: The pharmacokinetics of PegIntron following a single subcutaneous dose of 1.0 microgram/kg were not affected by age. The data suggest that no alteration in PegIntron dosage is necessary based on advancing age.

Patients under the age of 18 years: Specific pharmacokinetic evaluations have not been performed on these patients. PegIntron is indicated for the treatment of chronic hepatitis C only in patients 18 years of age or older.

Interferon neutralising factors: Interferon neutralising factor assays were performed on serum samples of patients who received PegIntron in the clinical trial. Interferon neutralising factors are antibodies which neutralise the antiviral activity of interferon. The clinical incidence of neutralising factors in patients who received PegIntron 0.5 micrograms/kg is 1.1 %.

5.3 Preclinical safety data

PegIntron: Adverse events not observed in clinical trials were not seen in toxicity studies in monkeys. These studies were limited to four weeks due to the appearance of anti-interferon antibodies in most monkeys.

Reproduction studies of PegIntron have not been performed. Interferon alfa-2b has been shown to be an abortifacient in primates. PegIntron is likely to also cause this effect. Effects on fertility have not been determined. PegIntron showed no genotoxic potential. (see section **4.6** for relevant human data. It is not known whether the components of this medicinal product are excreted in human milk. Therefore, nursing must be discontinued prior to the initiation of therapy.)

The relative non-toxicity of monomethoxy-polyethylene glycol (mPEG), which is liberated from PegIntron by metabolism *in vivo* has been demonstrated in preclinical acute and subchronic toxicity studies in rodents and monkeys, standard embryo-foetal development studies and in *in vitro* mutagenicity assays.

PegIntron plus ribavirin: When used in combination with ribavirin, PegIntron did not cause any effects not previously seen with either active substance alone. The major treatment-related change was a reversible, mild to moderate anaemia, the severity of which was greater than that produced by either active substance alone.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder for solution for injection:
Disodium phosphate, anhydrous,
Sodium dihydrogen phosphate dihydrate,
Sucrose,
Polysorbate 80.
Solvent for parenteral use:
Water for injections.

6.2 Incompatibilities

This medicinal product should only be reconstituted with the solvent provided and must not be mixed with other medicinal products (see also section **6.6**).

6.3 Shelf life

3 years

After reconstitution:
- Chemical and physical in-use stability has been demonstrated for 24 hours at 2°C - 8ºC.
- From a microbiological point of view, the product is to be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C - 8°C.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).

6.5 Nature and contents of container

The powder is contained in a 2 ml vial, Type I flint glass, with a butyl rubber stopper in an aluminium flip-off seal with a polypropylene bonnet. The solvent is presented in a 2 ml ampoule, Type I flint glass. PegIntron 80 micrograms is supplied as:
- 1 vial of powder for solution for injection and 1 ampoule of solvent for parenteral use;
- 1 vial of powder for solution for injection, 1 ampoule of solvent for parenteral use, 1 injection syringe, 2 injection needles and 1 cleansing swab;
- 4 vials of powder for solution for injection and 4 ampoules of solvent for parenteral use;
- 4 vials of powder for solution for injection, 4 ampoules of solvent for parenteral use, 4 injection syringes, 8 injection needles and 4 cleansing swabs;
- 6 vials of powder for solution for injection and 6 ampoules of solvent for parenteral use.
- 12 vials of powder for solution for injection, 12 ampoules of solvent for parenteral use, 12 injection syringes, 24 injection needles and 12 cleansing swabs.

Not all pack sizes may be marketed

6.6 Instructions for use and handling, and disposal

PegIntron is supplied as a powder of peginterferon alfa-2b at a strength of 80 micrograms for single use. Each vial must be reconstituted with 0.7 ml of water for injections for administration of up to 0.5 ml of solution. A small volume is lost during preparation of PegIntron for injection when the dose is measured and injected. Therefore, each vial contains an excess amount of solvent and PegIntron powder to ensure delivery of the labelled dose in 0.5 ml of PegIntron, solution for injection. The reconstituted solution has a concentration of 80 micrograms/0.5 ml.

Using a sterilised injection syringe and injection needle, inject 0.7 ml of water for injections into the vial of PegIntron. Agitate gently to complete dissolution of powder. The appropriate dose can then be withdrawn with a sterilised injection syringe and injected.

As for all parenteral medicinal products, inspect visually the reconstituted solution prior to administration. The reconstituted solution should be clear and colourless. Do not use if discolouration or particulate matter is present. Discard any unused material.

7. MARKETING AUTHORISATION HOLDER

SP Europe
73, rue de Stalle
B-1180 Bruxelles
Belgium

8. MARKETING AUTHORISATION NUMBERS

EU/1/00/131/006
EU/1/00/131/007
EU/1/00/131/008
EU/1/00/131/009
EU/1/00/131/010
EU/1/00/131/027

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

25 May 2000

10. DATE OF REVISION OF THE TEXT

1. NAME OF THE MEDICINAL PRODUCT

PegIntron 100 micrograms powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of PegIntron, powder for solution for injection contains 100 micrograms of peginterferon alfa-2b as measured on a protein basis.
Each vial provides 100 micrograms/0.5 ml of peginterferon alfa-2b when reconstituted as recommended.

The active substance is a covalent conjugate of recombinant interferon alfa-2b* with monomethoxy polyethylene glycol. The potency of this product should not be compared to that of another pegylated or non-pegylated protein of the same therapeutic class. For more information, see section **5.1.**
*produced by rDNA technology in *E.coli* cells harbouring a genetically engineered plasmid hybrid encompassing an interferon alfa-2b gene from human leukocytes

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection
The white powder is contained in a 2 ml glass vial and the clear and colourless solvent is presented in a 2 ml glass ampoule.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PegIntron is indicated for the treatment of adult patients with chronic hepatitis C who have elevated transaminases without liver decompensation and who are positive for serum HCV-RNA or anti-HCV (see section **4.4**).

The best way to use PegIntron in this indication is in combination with ribavirin.

This combination is indicated in naïve patients as well as in patients who have previously responded (with normalisation of ALT at the end of treatment) to interferon alpha monotherapy but who have subsequently relapsed.

Interferon monotherapy, including PegIntron, is indicated mainly in case of intolerance or contraindication to ribavirin.

Please refer also to the ribavirin Summary of Product Characteristics (SPC) when PegIntron is to be used in combination with ribavirin.

4.2 Posology and method of administration

Treatment should be initiated and monitored only by a physician experienced in the management of patients with hepatitis C.

Dose to be administered
PegIntron should be administered as a once weekly subcutaneous injection. The dose administered depends on whether it is used in combination with ribavirin or as monotherapy.

Combination therapy
PegIntron 1.5 micrograms/kg/week in combination with ribavirin capsules.

The intended dose of 1.5 μg/kg of PegIntron to be used in combination with ribavirin may be delivered in weight categories with the pen/vial strengths according to **Table 1**. Ribavirin capsules are to be administered orally each day in two divided doses with food (morning and evening).

Table 1 - Dosing for Combination Therapy

Body Weight (kg)	PegIntron		Ribavirin Capsules	
	Vial/Pen Strength (μg/0.5ml)	Administer Once Weekly (ml)	Total Daily Dose (mg)	Number of Capsules (200 mg)
< 40	50	0.5	800	4[a]
40-50	80	0.4	800	4[a]
51-64	80	0.5	800	4[a]
65-75	100	0.5	1,000	5[b]
76-85	120	0.5	1,000	5[b]
> 85	150	0.5	1,200	6[c]

a: 2 morning, 2 evening
b: 2 morning, 3 evening
c: 3 morning, 3 evening

Duration of treatment
Predictability of sustained virological response: Patients infected with virus genotype 1 who fail to achieve virological response at Week 12 are highly unlikely to become sustained virological responders (see also section **5.1**).

- **Genotype 1**: For patients who exhibit virological response at week 12, treatment should be continued for another nine month period (i.e., a total of 48 weeks).
- **Genotypes 2 or 3**: It is recommended that all patients be treated for 24 weeks.
- **Genotype 4:** In general, patients infected with genotype 4 are considered harder to treat and limited study data (n=66) indicate they are compatible with a posology as for genotype 1.

PegIntron monotherapy
As monotherapy the PegIntron regimen is 0.5 or 1.0 microgram/kg/week. The lowest vial or pen strength available is 50 μg/0.5 ml; therefore for patients prescribed 0.5 μg/kg/week, doses must be adjusted by volume as shown in **Table 2**. For the 1.0 μg/kg dose, similar volume adjustments can be made or alternate vial strengths can be used as shown in **Table 2**.

Table 2- Monotherapy Dosing

	0.5 μg/kg		1.0 μg/kg	
Body Weight (kg)	Vial/Pen Strength (μg/0.5ml)	Administer Once Weekly (ml)	Vial/Pen Strength (μg/0.5ml)	Administer Once Weekly (ml)
30-35	50*	0.15	50	0.3
36-45	50*	0.2	50	0.4
46-56	50*	0.25	50	0.5
57-72	50	0.3	80	0.4
73-88	50	0.4	80	0.5

89-106	50	0.5	100	0.5
> 106**	80	0.4	120	0.5
* Must use vial. Minimum delivery for pen is 0.3 ml. ** For patients > 120 kg, use 80 µg/0.5 ml vial				

Duration of treatment
For patients who exhibit virological response at Week 12, treatment should be continued for at least another three-month period (i.e., a total of six months). The decision to extend therapy to one year of treatment should be based on prognostic factors (e.g., genotype, age > 40 years, male gender, bridging fibrosis).

Dose modification for all patients
If severe adverse reactions or laboratory abnormalities develop during treatment with PegIntron monotherapy or PegIntron in combination with ribavirin, modify the dosages of each product as appropriate, until the adverse reactions abate. Guidelines were developed in clinical trials for dose modification.

Combination Therapy Dose Reduction Guidelines

Table 2a Dose modification guidelines for combination therapy (with ribavirin)

Laboratory values	**Reduce only ribavirin dose to 600 mg/day* if:**	**Reduce only PegIntron dose to one-half dose if:**	**Discontinue combination therapy if:**
Haemoglobin	< 10 g/dl	-	< 8.5 g/dl
Haemoglobin in: Patients with history of stable cardiac disease	≥ 2 g/dl decrease in haemoglobin during any four week period during treatment (permanent dose reduction)		< 12 g/dl after four weeks of dose reduction
White blood cells	-	< 1.5 x 10^9/l	< 1.0 x 10^9/l
Neutrophils	-	< 0.75 x 10^9/l	< 0.5 x 10^9/l
Platelets	-	< 50 x 10^9/l	< 25 x 10^9/l
Bilirubin – direct	-	-	2.5 x ULN**
Bilirubin - indirect	> 5 mg/dl	-	> 4 mg/dl (for > 4 weeks)
Creatinine	-	-	> 2.0 mg/dl
ALT/AST	-	-	2 x baseline and > 10 x ULN**

* Patients whose dose of ribavirin is reduced to 600 mg daily receive one 200 mg capsule in the morning and two 200 mg capsules in the evening.

** Upper limit of normal

Dose reduction of PegIntron may be accomplished by either reducing the prescribed volume by one-half or by utilizing a lower dose strength as shown in **Table 2b**.

Table 2b – Reduced PegIntron Dosing for Combination Therapy

Body Weight (kg)	**Target Reduced Dose (µg)**	**Vial/Pen Strength (µg/0.5 ml)**	**Administer Once Weekly (ml)**	**Amount Delivered (µg)**
< 40	25	50*	0.25	25
40-50	32	50	0.3	30
51-64	40	50	0.4	40
65-75	50	50	0.5	50

76-85	60	80	0.4	64
> 85	75	100	0.4	80
*Must use vial. Minimum delivery for pen is 0.3 ml.				

PegIntron Monotherapy Dose Reduction Guidelines

Dose modification guidelines for patients who use PegIntron monotherapy are shown in **Table 3a.**

Table 3a Dose modification guidelines for PegIntron monotherapy		
Laboratory values	**Reduce PegIntron to one-half dose if:**	**Discontinue PegIntron if:**
Neutrophils	< 0.75 x 10^9/l	< 0.5 x 10^9/l
Platelets	< 50 x 10^9/l	< 25 x 10^9/l

Dose reduction for patients who use 0.5 µg/kg PegIntron monotherapy must be accomplished by reducing the prescribed volume by one-half. The 50 µg/0.5 ml vial must be used if necessary since the pen can only deliver a minimum volume of 0.3 ml.

For patients who use 1.0 µg/kg PegIntron monotherapy, dose reduction may be accomplished by reducing the prescribed volume by one-half or by utilizing a lower dose strength as shown in **Table 3b**.

Table 3b – Reduced PegIntron Dose for the 1.0 µg/kg Monotherapy Regimen				
Body Weight (kg)	**Target Reduced Dose (µg)**	**Vial/Pen Strength (µg/0.5ml)**	**Administer Once Weekly (ml)**	**Amount Delivered (µg)**
30-35	15	50*	0.15	15
36-45	20	50*	0.20	20
46-56	25	50*	0.25	25
57-72	32	50	0.3	30
73-89	40	50	0.4	40
90-106	50	50	0.5	50
> 106	60	80	0.4	64
*Must use vial. Minimum delivery for pen is 0.3 ml.				

Special populations

Use in renal impairment: The clearance of PegIntron is reduced in patients with significant renal impairment. Patients with creatinine clearance ≤ 50 ml/minute must not be treated with PegIntron (see section **5.2**). It is recommended that patients with moderate renal impairment be closely monitored and that their weekly dose of PegIntron be reduced if medically appropriate.

Use in hepatic impairment: The safety and efficacy of PegIntron therapy has not been evaluated in patients with severe hepatic dysfunction, therefore PegIntron must not be used for these patients.

Use in the elderly (≥ 65 years of age): There are no apparent age-related effects on the pharmacokinetics of PegIntron. Data from elderly patients treated with a single dose of PegIntron suggest no alteration in PegIntron dose is necessary based on age (see section **5.2**).

Use in patients under the age of 18 years: PegIntron is not recommended for use in children or adolescents under the age of 18, as there is no experience in this group.

4.3 Contraindications

- Hypersensitivity to the active substance or to any interferon or to any of the excipients;
- Pregnant women;
- Women who are breast-feeding;
- A history of severe pre-existing cardiac disease, including unstable or uncontrolled cardiac disease in the previous six months (see section **4.4**);
- Severe, debilitating medical conditions, including patients with chronic renal failure or creatinine clearance < 50 ml/minute;
- Autoimmune hepatitis or a history of autoimmune disease;
- Severe hepatic dysfunction or decompensated cirrhosis of the liver;
- Pre-existing thyroid disease unless it can be controlled with conventional treatment;
- Epilepsy and/or compromised central nervous system (CNS) function.

4.4 Special warnings and special precautions for use

There is no experience with PegIntron in combination with ribavirin in patients who have relapsed after interferon alpha + ribavirin therapy.

All patients in the chronic hepatitis C studies had a liver biopsy before inclusion, but in certain cases (i.e. patients with genotype 2 and 3), treatment may be possible without histological confirmation. Current treatment guidelines should be consulted as to whether a liver biopsy is needed prior to commencing treatment.

Acute hypersensitivity: Acute hypersensitivity reactions (e.g., urticaria, angioedema, bronchoconstriction, anaphylaxis) have been observed rarely during interferon alfa-2b therapy. If such a reaction develops during treatment with PegIntron, discontinue treatment and institute appropriate medical therapy immediately. Transient rashes do not necessitate interruption of treatment.

Cardiovascular system: As with interferon alfa-2b, patients with a history of congestive heart failure, myocardial infarction and/or previous or current arrhythmic disorders, receiving PegIntron therapy require close monitoring. It is recommended that patients who have pre-existing cardiac abnormalities have electrocardiograms taken prior to and during the course of treatment. Cardiac arrhythmias (primarily supraventricular) usually respond to conventional therapy but may require discontinuation of PegIntron therapy.

Psychiatric and Central Nervous System (CNS): If treatment with peginterferon alfa-2b is judged necessary in patients with existence or history of severe psychiatric conditions, this should only be initiated after having ensured appropriate individualised diagnostic and therapeutic management of the psychiatric condition.
Severe CNS effects, particularly depression, suicidal ideation and attempted suicide have been observed in some patients during PegIntron therapy. Other CNS effects including aggressive behaviour, confusion and alterations of mental status have been observed with alpha interferon. If patients develop psychiatric or CNS problems, including clinical depression, it is recommended that the patient be carefully monitored due to the potential seriousness of these undesirable effects. If symptoms persist or worsen, discontinue PegIntron therapy.
More significant obtundation and coma, including cases of encephalopathy, have been observed in some patients, usually elderly, treated at higher doses for oncology indications. While these effects are generally reversible, in a few patients full resolution took up to three weeks. Very rarely, seizures have occurred with high doses of interferon alpha.

Liver function: As with all interferons, discontinue treatment with PegIntron in patients who develop prolongation of coagulation markers which might indicate liver decompensation.

Fever: While fever may be associated with the flu-like syndrome reported commonly during interferon therapy, other causes of persistent fever must be ruled out.

Hydration: Adequate hydration must be maintained in patients undergoing PegIntron therapy since hypotension related to fluid depletion has been seen in some patients treated with alpha interferons. Fluid replacement may be necessary.

Pulmonary changes: Pulmonary infiltrates, pneumonitis, and pneumonia, occasionally resulting in fatality, have been observed rarely in interferon alpha treated patients. Any patient developing fever, cough, dyspnea or other respiratory symptoms must have a chest X-ray taken. If the chest X-ray shows pulmonary infiltrates or there is evidence of pulmonary function impairment, the patient is to be monitored closely, and, if appropriate, discontinue interferon alpha. Prompt discontinuation of interferon alpha administration and treatment with corticosteroids appear to be associated with resolution of pulmonary adverse events.

Autoimmune disease: The development of auto-antibodies and autoimmune disorders has been reported during treatment with alpha interferons. Patients predisposed to the development of autoimmune disorders may be at increased risk. Patients with signs or symptoms compatible with autoimmune disorders should be evaluated carefully, and the benefit-risk of continued interferon therapy should be reassessed (see also section **4.4 Thyroid changes** and **4.8**).

Ocular changes: Ophthalmologic disorders, including retinal haemorrhages, cotton wool spots, and retinal artery or vein obstruction have been reported in rare instances after treatment with alpha interferons (see section **4.8**). All patients should have a baseline eye examination. Any patient complaining of ocular symptoms, including loss of visual acuity or visual field must have a prompt and complete eye examination. Periodic visual examinations are recommended during PegIntron therapy, particularly in patients with disorders that may be associated with retinopathy, such as diabetes mellitus or hypertension. Discontinuation of PegIntron should be considered in patients who develop new or worsening ophthalmological disorders.

Thyroid changes: Infrequently, patients treated for chronic hepatitis C with interferon alpha have developed thyroid abnormalities, either hypothyroidism or hyperthyroidism. Determine thyroid stimulating hormone (TSH) levels if, during the course of therapy, a patient develops symptoms consistent with possible thyroid dysfunction. In the presence of thyroid dysfunction, PegIntron treatment may be continued if TSH levels can be maintained in the normal range by medication.

Metabolic disturbances: Hypertriglyceridemia and aggravation of hypertriglyceridemia, sometimes severe, have been observed. Monitoring of lipid levels is, therefore, recommended.

HCV/HIV Coinfection
Patients co-infected with HIV and receiving Highly Active Anti-Retroviral Therapy (HAART) may be at increased risk of developing lactic acidosis. Caution should be used when adding PegIntron and ribavirin to HAART therapy (see ribavirin SPC).
Co-infected patients with advanced cirrhosis receiving HAART may be at increased risk of hepatic decompensation and death. Adding treatment with alfa interferons alone or in combination with ribavirin may increase the risk in this patient subset.

Organ transplant recipients: The safety and efficacy of PegIntron alone or in combination with ribavirin for the treatment of hepatitis C in liver or other organ transplant recipients have not been studied. Preliminary data indicates that interferon alpha therapy may be associated with an increased rate of kidney graft rejection. Liver graft rejection has also been reported.

Other: Due to reports of interferon alpha exacerbating pre-existing psoriatic disease and sarcoidosis, use of PegIntron in patients with psoriasis or sarcoidosis is recommended only if the potential benefit justifies the potential risk.

Laboratory tests: Standard haematologic tests, blood chemistry and a test of thyroid function must be conducted in all patients prior to initiating therapy. Acceptable baseline values that may be considered as a guideline prior to initiation of PegIntron therapy are:

- Platelets ≥ 100,000/mm^3
- Neutrophil count ≥ 1,500/mm^3
- TSH level must be within normal limits

Laboratory evaluations are to be conducted at weeks 2 and 4 of therapy, and periodically thereafter as clinically appropriate.

4.5 Interaction with other medicinal products and other forms of interaction

Results of a single-dose study with PegIntron demonstrated no effect on the activity of cytochrome (CY) P1A2, CYP2C8/9, CYP2D6, and hepatic CYP3A4 or N-acetyl transferase. Caution should be advised in the interpretation of these results as the use of other forms of interferon alpha result in a 50 % reduction in the clearance and thus a doubling of plasma concentrations of theophylline, a substrate of CYP1A2.

No pharmacokinetic interactions were noted between PegIntron and ribavirin in a multiple-dose pharmacokinetic study.

4.6 Pregnancy and lactation

There are no adequate data on the use of interferon alfa-2b in pregnant women. Interferon alfa-2b has been shown to be abortifacient in primates. PegIntron is likely to also cause this effect. PegIntron should not be used during pregnancy (see section **5.3**).

PegIntron is recommended for use in fertile women only when they are using effective contraception during the treatment period.

Lactation: It is not known whether the components of this medicinal product are excreted in human milk. Because of the potential for adverse reactions in nursing infants, nursing must be discontinued prior to initiation of treatment.

Ribavirin is teratogenic and embryocidal and must not be used in pregnant women (see ribavirin SPC, **5.3**).

4.7 Effects on ability to drive and use machines

Patients who develop fatigue, somnolence or confusion during treatment with PegIntron are cautioned to avoid driving or operating machinery.

4.8 Undesirable effects

The safety of PegIntron is evaluated from data from two clinical trials: one with PegIntron monotherapy, one with PegIntron in combination with ribavirin. In both cases, patients were treated for one year.

Table 4 describes the regimens and patient exposure for one year of treatment in patients with no previous exposure to interferon (interferon-naïve patients). Because of a significant overlap in the pattern of undesirable effects with PegIntron monotherapy, groups of patients have been brought together in **Table 5** to show the pattern of reported effects for all monotherapy groups.

Table 4	Regimens and patient exposure	
Treatment	**Regimen**	**Number of patients treated for one year**
PegIntron + ribavirin	PegIntron (1.5 micrograms/kg/week) + ribavirin (> 10.6 mg/kg/day)	188
Interferon alfa-2b + ribavirin	Interferon alfa-2b (3 MIU three times a week) + ribavirin (1,000/1,200 mg/day)	505
PegIntron monotherapy	PegIntron (0.5 microgram/kg/week)	315
	PegIntron (1.0 microgram/kg/week)	297
	PegIntron (1.5 micrograms/kg/week)	304

Table 5 Undesirable effects reported in clinical trials (≥ 10 % of patients in PegIntron + ribavirin group)			
	PegIntron + ribavirin	**Interferon alfa-2b + ribavirin**	**PegIntron monotherapy**
Application site disorder			
Injection site inflammation	20 %	17 %	39-44 %
Injection site reaction	54 %	36 %	7-9 %
Body as a whole			
Headache	58 %	57 %	57-63 %
Fatigue	56 %	59 %	43 %
Rigors	42 %	40 %	33-43 %
Fever	39 %	32 %	29-43 %
Flu-like symptoms	21 %	23 %	18-25 %
Asthenia	28 %	17 %	12-14 %
Weight decrease	30 %	19 %	8-18 %
Gastrointestinal			
Nausea	43 %	31 %	20-23 %
Anorexia	35 %	26 %	10-25 %
Diarrhoea	20 %	13 %	14-17 %
Abdominal pain	12 %	9 %	11 %
Vomiting	16 %	10 %	4-7 %
Musculoskeletal			
Myalgia	49 %	49 %	46-60 %
Arthralgia	31 %	26 %	23-28 %
Musculoskeletal pain	15 %	11 %	11-13 %
Psychiatric			
Depression	34 %	32 %	26 %
Irritability	32 %	34 %	19 %
Insomnia	37 %	41 %	16-19 %
Anxiety	14 %	14 %	8 %
Concentration impaired	18 %	21 %	9-10 %
Emotional lability	11 %	10 %	5 %
Respiratory system			
Pharyngitis	10 %	7 %	3 %
Coughing	14 %	11 %	4 %
Dyspnea	26 %	22 %	5 %
Skin and appendages			
Alopecia	45 %	32 %	20-34 %
Pruritus	27 %	27 %	7-9 %
Skin dry	23 %	21 %	6-9 %
Rash	21 %	21 %	5-7 %
Other			
Dizziness	17 %	16 %	7-12 %
Infection viral	10 %	5 %	4-5 %
Mouth dry	10 %	8 %	4-8 %

Table 6 Undesirable effects reported in clinical trials (1%-< 10% of patients treated with PegIntron + ribavirin or PegIntron monotherapy)		
Body system	**5-10%**	**1-<5%**
Body as a whole	chest pain, RUQ pain, malaise	erythema, injection site pain, flushing, thirst, herpes simplex, face or peripheral oedema, dehydration
Cardiovascular		tachycardia, palpitation, hypotension, hypertension, syncope
Central/peripheral nervous system	paresthesia	hypoaesthesia, hyperaesthesia, hypertonia, decreased libido, confusion, tremor, vertigo, migraine, tinnitus, hearing impairment/loss, ataxia, neuralgia
Endocrine	hypothyroidism,	hyperthyroidism, amenorrhoea, prostatitis, hyperuricemia, hypocalcemia
Gastrointestinal	dyspepsia,	constipation, taste perversion, loose stools, stomatitis, ulcerative stomatitis, gingival bleeding, glossitis, flatulence, hemorrhoids, gastroesophageal reflux, hepatomegaly, bilirubinemia, gingivitis
Haematologic	anaemia, leukopaenia	thrombocytopenia, lymphadenopathy,
Musculoskeletal		arthritis
Ocular		blurred vision, conjunctivitis, lacrimal gland disorder, eye pain
Psychiatric	agitation, nervousness	aggressive behaviour, somnolence, behavior disorder, apathy, appetite increased, sleep disorder, dreaming abnormal
Reproductive	menstrual disorder, menorrhagia	ovarian disorder, vaginal disorder, sexual dysfunction (not specified), impotence, breast pain
Respiratory		nonproductive cough, rhinitis, sinusitis, bronchitis, respiratory disorder, nasal congestion, rhinorrhea, dysphonia, epistaxis
Resistance mechanism		otitis media, fungal infection, bacterial infection
Skin and appendages	increased sweating	erythematous rash, eczema, photosensitivity reaction, maculopapular rash, abnormal hair texture, acne, dermatitis, furunculosis, nail disorder, psoriasis, urticaria
Urinary		micturition frequency, urine abnormal

Most cases of neutropaenia and thrombocytopaenia were mild (WHO grades 1 or 2). There were some cases of more severe neutropenia in patients treated with the recommended doses of PegIntron in combination with ribavirin (WHO grade 3: 39 of 186 [21 %]; and WHO grade 4: 13 of 186 [7 %]).

In a clinical trial, approximately 1.2 % of patients treated with PegIntron or interferon alfa-2b in combination with ribavirin reported life-threatening psychiatric events during treatment. These events included suicidal ideation and attempted suicide (see section **4.4)**. Following marketing, psychosis and hallucination have been reported rarely.

Rarely reported events with interferon alfa-2b, including PegIntron, include seizure, pancreatitis, arrhythmia, peripheral neuropathy, diabetes, rhabdomyolysis, myositis, renal insufficiency and renal failure.

Cardiovascular (CVS) adverse events, particularly arrhythmia, appeared to be correlated mostly with pre-existing CVS disease and prior therapy with cardiotoxic agents (see section **4.4**). Cardiomyopathy, that may be reversible upon discontinuation of interferon alpha, has been reported rarely in patients without prior evidence of cardiac disease.

Very rarely cases of erythema multiforme, Stevens Johnson syndrome, toxic epidermal necrolysis, cardiac ischaemia, myocardial infarction, cerebrovascular ischaemia, cerebrovascular hemorrhage, encephalopathy, sarcoidosis or exacerbation of sarcoidosis, interstitial lung disease and injection site necrosis have been reported. Ulcerative and ischaemic colitis have been reported very rarely with PegIntron.

Very rarely, interferon alfa-2b or PegIntron used alone or in combination with ribavirin may be associated with aplastic anaemia.

Ophthalmological disorders that have been reported rarely with alpha interferons include retinopathies (including macular oedema), retinal haemorrhages, retinal artery or vein obstruction, cotton wool spots, loss of visual acuity or visual field, optic neuritis, and papilloedema (see section **4.4**).

A wide variety of autoimmune and immune-mediated disorders have been reported with alpha interferons including thyroid disorders, idiopathic and thrombotic thrombocytopenic purpura, vasculitis, neuropathies including mononeuropathies (see also section **4.4**, **Autoimmune disorders**).

4.9 Overdose

In clinical trials, cases of accidental overdose, at never more than twice the prescribed dose, were reported. There were no serious reactions. Undesirable effects resolved during continued administration of PegIntron.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunostimulants, Cytokines and immunomodulators, Interferons, Peginterferon alfa-2b, ATC code: L03A B10.

Recombinant interferon alfa-2b is covalently conjugated with monomethoxy polyethylene glycol at an average degree of substitution of 1 mole of polymer/mole of protein. The average molecular mass is approximately 31,300 daltons of which the protein moiety constitutes approximately 19,300.

Interferon alfa-2b
In vitro and *in vivo* studies suggest that the biological activity of PegIntron is derived from its interferon alfa-2b moiety.

Interferons exert their cellular activities by binding to specific membrane receptors on the cell surface. Studies with other interferons have demonstrated species specificity. However, certain monkey species, e.g., Rhesus monkeys, are susceptible to pharmacodynamic stimulation upon exposure to human type 1 interferons.

Once bound to the cell membrane, interferon initiates a complex sequence of intracellular events that include the induction of certain enzymes. It is thought that this process, at least in part, is responsible for the various cellular responses to interferon, including inhibition of virus replication in virus-infected cells, suppression of cell proliferation and such immunomodulating activities as enhancement

of the phagocytic activity of macrophages and augmentation of the specific cytotoxicity of lymphocytes for target cells. Any or all of these activities may contribute to interferon's therapeutic effects.

Recombinant interferon alfa-2b also inhibits viral replication *in vitro* and *in vivo*. Although the exact antiviral mode of action of recombinant interferon alfa-2b is unknown, it appears to alter the host cell metabolism. This action inhibits viral replication or if replication occurs, the progeny virions are unable to leave the cell.

PegIntron
PegIntron pharmacodynamics were assessed in a rising single-dose trial in healthy subjects by examining changes in oral temperature, concentrations of effector proteins such as serum neopterin and 2'5'-oligoadenylate synthetase (2'5'-OAS), as well as white cell and neutrophil counts. Subjects treated with PegIntron showed mild dose-related elevations in body temperature. Following single doses of PegIntron between 0.25 and 2.0 micrograms/kg/week, serum neopterin concentration was increased in a dose-related manner. Neutrophil and white cell count reductions at the end of week 4 correlated with the dose of PegIntron.

PegIntron clinical trials
Two pivotal trials have been conducted, one (C/I97-010) with PegIntron monotherapy; the other (C/I98-580) with PegIntron in combination with ribavirin. Eligible patients for these trials had chronic hepatitis C confirmed by a positive HCV-RNA polymerase chain reaction (PCR) assay (> 30 IU/ml), a liver biopsy consistent with a histological diagnosis of chronic hepatitis with no other cause for the chronic hepatitis, and abnormal serum ALT.

In the PegIntron monotherapy trial, a total of 916 naïve chronic hepatitis C patients were treated with PegIntron (0.5, 1.0 or 1.5 micrograms/kg/week) for one year with a follow-up period of six months. In addition, 303 patients received interferon alfa-2b (3 million International Units [MIU] three times a week as a comparator. This study showed that PegIntron was superior to interferon alfa-2b (**Table 7**).

In the PegIntron combination trial, 1,530 naïve patients were treated for one year with one of the following combination regimens:
- PegIntron (1.5 micrograms/kg/week) + ribavirin (800 mg/day), (n = 511).
- PegIntron (1.5 micrograms/kg/week for one month followed by 0.5 microgram/kg/week for 11 months) + ribavirin (1,000/1,200 mg/day), (n = 514).
- Interferon alfa-2b (3 MIU three times a week) + ribavirin (1,000/1,200 mg/day) (n = 505).

In this trial, the combination of PegIntron (1.5 micrograms/kg/week) and ribavirin was significantly more effective than the combination of interferon alfa-2b and ribavirin (**Table 7**), particularly in patients infected with Genotype 1 (**Table 8**). Sustained response was assessed by the response rate six months after the cessation of treatment.

HCV genotype and baseline virus load are prognostic factors which are known to affect response rates. However, response rates in this trial were shown to be dependent also on the dose of ribavirin administered in combination with PegIntron or interferon alfa-2b. In those patients that received > 10.6 mg/kg ribavirin (800 mg dose in typical 75 kg patient), regardless of genotype or viral load, response rates were significantly higher than in those patients that received ≤ 10.6 mg/kg ribavirin (**Table 8**), while response rates in patients that received > 13.2 mg/kg ribavirin were even higher.

Table 7 Sustained virological response (% patients HCV negative)

	PegIntron monotherapy				**PegIntron + ribavirin**		
Treatment regimen	**P 1.5**	**P 1.0**	**P 0.5**	**I**	**P 1.5/R**	**P 0.5/R**	**I/R**
Number of patients	304	297	315	303	511	514	505
Response at end of treatment	49 %	41 %	33 %	24 %	65 %	56 %	54 %

Sustained response	**23 %***	**25 %**	**18 %**	**12 %**	**54 %****	**47 %**	**47 %**

P 1.5 PegIntron 1.5 micrograms/kg
P 1.0 PegIntron 1.0 microgram/kg
P 0.5 PegIntron 0.5 microgram/kg
I Interferon alfa-2b 3 MIU
P 1.5/R PegIntron (1.5 micrograms/kg) + ribavirin (800 mg)
P 0.5/R PegIntron (1.5 to 0.5 microgram/kg) + ribavirin (1,000/1,200 mg)
I/R Interferon alfa-2b (3 MIU) + ribavirin (1,000/1,200 mg)
* $p < 0.001$ P 1.5 vs. I
** $p = 0.0143$ P 1.5/R vs. I/R

Table 8 Sustained response rates with PegIntron + ribavirin (by ribavirin dose , genotype and viral load)

HCV Genotype	**Rebetol dose (mg/kg)**	**P 1.5/R**	**P 0.5/R**	**I/R**
All Genotypes	**All**	**54 %**	**47 %**	**47 %**
	≤ 10.6	50 %	41 %	27 %
	> 10.6	61 %	48 %	47 %
Genotype 1	**All**	**42 %**	**34 %**	**33 %**
	≤ 10.6	38 %	25 %	20 %
	> 10.6	48 %	34 %	34 %
Genotype 1 ≤ 600,000 IU/ml	All	73 %	51 %	45 %
	≤ 10.6	74 %	25 %	33 %
	> 10.6	71 %	52 %	45 %
Genotype 1 > 600,000 IU/ml	All	30 %	27 %	29 %
	≤ 10.6	27 %	25 %	17 %
	> 10.6	37 %	27 %	29 %
Genotype 2/3	**All**	**82 %**	**80 %**	**79 %**
	≤ 10.6	79 %	73 %	50 %
	> 10.6	88 %	80 %	80 %

P 1.5/R PegIntron (1.5 micrograms/kg) + ribavirin (800 mg)
P 0.5/R PegIntron (1.5 to 0.5 microgram/kg) + ribavirin (1,000/1,200 mg)
I/R Interferon alfa-2b (3 MIU) + ribavirin (1,000/1,200 mg)

In the PegIntron monotherapy study, the Quality of Life was generally less affected by 0.5 microgram/kg of PegIntron than by either 1.0 microgram/kg of PegIntron once weekly or 3 MIU of interferon alfa-2b three times a week.

In a separate trial, 224 patients with genotype 2 or 3 received PegIntron, 1.5 microgram/kg subcutaneously, once weekly, in combination with ribavirin 800 mg –1,400 mg p.o. for 6 months (based on body weight, only three patients weighing > 105 kg, received the 1,400 mg dose, which has not yet been validated) (**Table 9**). Twenty-four % had bridging fibrosis or cirrhosis (Knodell 3/4).

Table 9. Virologic Response at End of Treatment, Sustained Virologic Response and Relapse by HCV Genotype and Viral Load*

	PegIntron 1.5 μg/kg Once Weekly Plus Rebetol 800-1400 mg/day		
	End of Treatment Response	Sustained Virologic Response	Relapse
All Subjects	94 % (211/224)	81 % (182/224)	12 % (27/224)
HCV 2	100 % (42/42)	93 % (39/42)	7 % (3/42)
≤ 600,000 IU/ml	100 % (20/20)	95 % (19/20)	5 % (1/20)
> 600,000	100 % (22/22)	91 % (20/22)	9 % (2/22)

IU/mL			
HCV 3	93 % (169/182)	79 % (143/182)	14 % (24/166)
≤ 600,000 IU/ml	93 % (92/99)	86 % (85/99)	8 % (7/91)
> 600,000 IU/ml	93 % (77/83)	70 % (58/83)	23 % (17/75)

* Any subject with an undetectable HCV-RNA level at the Follow-Up Week 12 visit and missing data at the Follow-Up Week 24 visit was considered a sustained responder. Any subject with missing data in and after the Follow-Up Week 12 window was considered to be a non-responder at Week 24 of follow-up.

The 6 month treatment duration in this trial was better tolerated than one year of treatment in the pivotal combination trial; for discontinuation 5 % vs. 14 %, for dose modification 18 % vs. 49 %.

Predictability of sustained virological response
Virological reponse by week 12, defined as a 2-log viral load decrease or undetectable levels of HCV RNA has been shown to be predictive for sustained response (**Table 10**).

Table 10 Predictability of sustained response by viral response at week 12 and genotype*

Treatment	Genotype	Viral response at week 12	Sustained response	Negative predictive value
PegIntron 1.5 + ribavirin (> 10.6 mg/kg) 48-week treatment	1	Yes 75 % (82/110)	71 % (58/82)	----
		No 25 % (28/110)	0 % (0/28)	100 %
PegIntron 1.5 + ribavirin 800-1,400 mg 24-week treatment	2 and 3	Yes 99 % (213/215)	83 % (177/213)	----
		No 1 % (2/215)	50 % (1/2)	50 %

* reflects patients with 12 week data available

The negative predictive value for sustained response in patients treated with PegIntron in monotherapy was 98 %.

5.2 Pharmacokinetic properties

PegIntron is a well characterized polyethylene glycol-modified (“pegylated”) derivative of interferon alfa-2b and is predominantly composed of monopegylated species. The plasma half-life of PegIntron is prolonged compared with non-pegylated interferon alfa-2b. PegIntron has a potential to depegylate to free interferon alfa-2b. The biologic activity of the pegylated isomers is qualitatively similar, but weaker than free interferon alfa-2b.

Following subcutaneous administration, maximal serum concentrations occur between 15-44 hours post-dose, and are sustained for up to 48-72 hours post-dose.

PegIntron C_{max} and AUC measurements increase in a dose-related manner. Mean apparent volume of distribution is 0.99 l/kg.

Upon multiple dosing, there is an accumulation of immunoreactive interferons. There is, however, only a modest increase in biologic activity as measured by a bioassay.

Mean (SD) PegIntron elimination half-life is approximately 40 hours (13.3 hours), with apparent clearance of 22.0 ml/hr·kg. The mechanisms involved in clearance of interferons in man have not yet been fully elucidated. However, renal elimination may account for a minority (approximately 30 %) of PegIntron apparent clearance.

Renal function: Renal clearance appears to account for 30 % of total clearance of PegIntron. In a single dose study (1.0 microgram/kg) in patients with impaired renal function, C_{max}, AUC, and half-life increased in relation to the degree of renal impairment.

Based on these data, no dose modification is recommended based on creatinine clearance. However, because of marked intra-subject variability in interferon pharmacokinetics, it is recommended that patients be monitored closely during treatment with PegIntron (see section **4.2**). Patients with severe renal dysfunction or creatinine clearance < 50 ml/min must not be treated with PegIntron.

Hepatic function: The pharmacokinetics of PegIntron have not been evaluated in patients with severe hepatic dysfunction.

Elderly patients ≥ 65 years of age: The pharmacokinetics of PegIntron following a single subcutaneous dose of 1.0 microgram/kg were not affected by age. The data suggest that no alteration in PegIntron dosage is necessary based on advancing age.

Patients under the age of 18 years: Specific pharmacokinetic evaluations have not been performed on these patients. PegIntron is indicated for the treatment of chronic hepatitis C only in patients 18 years of age or older.

Interferon neutralising factors: Interferon neutralising factor assays were performed on serum samples of patients who received PegIntron in the clinical trial. Interferon neutralising factors are antibodies which neutralise the antiviral activity of interferon. The clinical incidence of neutralising factors in patients who received PegIntron 0.5 micrograms/kg is 1.1 %.

5.3 Preclinical safety data

PegIntron: Adverse events not observed in clinical trials were not seen in toxicity studies in monkeys. These studies were limited to four weeks due to the appearance of anti-interferon antibodies in most monkeys.

Reproduction studies of PegIntron have not been performed. Interferon alfa-2b has been shown to be an abortifacient in primates. PegIntron is likely to also cause this effect. Effects on fertility have not been determined. PegIntron showed no genotoxic potential. (see section **4.6** for relevant human data. It is not known whether the components of this medicinal product are excreted in human milk. Therefore, nursing must be discontinued prior to the initiation of therapy.)

The relative non-toxicity of monomethoxy-polyethylene glycol (mPEG), which is liberated from PegIntron by metabolism *in vivo* has been demonstrated in preclinical acute and subchronic toxicity studies in rodents and monkeys, standard embryo-foetal development studies and in *in vitro* mutagenicity assays.

PegIntron plus ribavirin: When used in combination with ribavirin, PegIntron did not cause any effects not previously seen with either active substance alone. The major treatment-related change was a reversible, mild to moderate anaemia, the severity of which was greater than that produced by either active substance alone.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder for solution for injection:
Disodium phosphate, anhydrous,
Sodium dihydrogen phosphate dihydrate,
Sucrose,
Polysorbate 80.
Solvent for parenteral use:
Water for injections.

6.2 Incompatibilities

This medicinal product should only be reconstituted with the solvent provided and must not be mixed with other medicinal products (see also section **6.6**).

6.3 Shelf life

3 years

After reconstitution:
- Chemical and physical in-use stability has been demonstrated for 24 hours at 2°C - 8ºC.
- From a microbiological point of view, the product is to be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C - 8°C.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).

6.5 Nature and contents of container

The powder is contained in a 2 ml vial, Type I flint glass, with a butyl rubber stopper in an aluminium flip-off seal with a polypropylene bonnet. The solvent is presented in a 2 ml ampoule, Type I flint glass. PegIntron 100 micrograms is supplied as:
- 1 vial of powder for solution for injection and 1 ampoule of solvent for parenteral use;
- 1 vial of powder for solution for injection, 1 ampoule of solvent for parenteral use, 1 injection syringe, 2 injection needles and 1 cleansing swab;
- 4 vials of powder for solution for injection and 4 ampoules of solvent for parenteral use;
- 4 vials of powder for solution for injection, 4 ampoules of solvent for parenteral use, 4 injection syringes, 8 injection needles and 4 cleansing swabs;
- 6 vials of powder for solution for injection and 6 ampoules of solvent for parenteral use.
- 12 vials of powder for solution for injection, 12 ampoules of solvent for parenteral use, 12 injection syringes, 24 injection needles and 12 cleansing swabs.

Not all pack sizes may be marketed

6.6 Instructions for use and handling, and disposal

PegIntron is supplied as a powder of peginterferon alfa-2b at a strength of 100 micrograms for single use. Each vial must be reconstituted with 0.7 ml of water for injections for administration of up to 0.5 ml of solution. A small volume is lost during preparation of PegIntron for injection when the dose is measured and injected. Therefore, each vial contains an excess amount of solvent and PegIntron powder to ensure delivery of the labelled dose in 0.5 ml of PegIntron, solution for injection. The reconstituted solution has a concentration of 100 micrograms/0.5 ml.

Using a sterilised injection syringe and injection needle, inject 0.7 ml of water for injections into the vial of PegIntron. Agitate gently to complete dissolution of powder. The appropriate dose can then be withdrawn with a sterilised injection syringe and injected.

As for all parenteral medicinal products, inspect visually the reconstituted solution prior to administration. The reconstituted solution should be clear and colourless. Do not use if discolouration or particulate matter is present. Discard any unused material.

7. MARKETING AUTHORISATION HOLDER

SP Europe
73, rue de Stalle
B-1180 Bruxelles
Belgium

8. MARKETING AUTHORISATION NUMBERS

EU/1/00/131/011
EU/1/00/131/012
EU/1/00/131/013
EU/1/00/131/014
EU/1/00/131/015
EU/1/00/131/028

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

25 May 2000

10. DATE OF REVISION OF THE TEXT

1. NAME OF THE MEDICINAL PRODUCT

PegIntron 120 micrograms powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of PegIntron, powder for solution for injection contains 120 micrograms of peginterferon alfa-2b as measured on a protein basis.
Each vial provides 120 micrograms/0.5 ml of peginterferon alfa-2b when reconstituted as recommended.

The active substance is a covalent conjugate of recombinant interferon alfa-2b* with monomethoxy polyethylene glycol. The potency of this product should not be compared to that of another pegylated or non-pegylated protein of the same therapeutic class. For more information, see section **5.1.**
*produced by rDNA technology in *E.coli* cells harbouring a genetically engineered plasmid hybrid encompassing an interferon alfa-2b gene from human leukocytes

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection
The white powder is contained in a 2 ml glass vial and the clear and colourless solvent is presented in a 2 ml glass ampoule.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PegIntron is indicated for the treatment of adult patients with chronic hepatitis C who have elevated transaminases without liver decompensation and who are positive for serum HCV-RNA or anti-HCV (see section **4.4**).

The best way to use PegIntron in this indication is in combination with ribavirin.

This combination is indicated in naïve patients as well as in patients who have previously responded (with normalisation of ALT at the end of treatment) to interferon alpha monotherapy but who have subsequently relapsed.

Interferon monotherapy, including PegIntron, is indicated mainly in case of intolerance or contraindication to ribavirin.

Please refer also to the ribavirin Summary of Product Characteristics (SPC) when PegIntron is to be used in combination with ribavirin.

4.2 Posology and method of administration

Treatment should be initiated and monitored only by a physician experienced in the management of patients with hepatitis C.

Dose to be administered
PegIntron should be administered as a once weekly subcutaneous injection. The dose administered depends on whether it is used in combination with ribavirin or as monotherapy.

Combination therapy
PegIntron 1.5 micrograms/kg/week in combination with ribavirin capsules.

The intended dose of 1.5 μg/kg of PegIntron to be used in combination with ribavirin may be delivered in weight categories with the pen/vial strengths according to **Table 1**. Ribavirin capsules are to be administered orally each day in two divided doses with food (morning and evening).

Table 1 - Dosing for Combination Therapy

Body Weight (kg)	PegIntron		Ribavirin Capsules	
	Vial/Pen Strength (μg/0.5ml)	Administer Once Weekly (ml)	Total Daily Dose (mg)	Number of Capsules (200 mg)
< 40	50	0.5	800	4[a]
40-50	80	0.4	800	4[a]
51-64	80	0.5	800	4[a]
65-75	100	0.5	1,000	5[b]
76-85	120	0.5	1,000	5[b]
> 85	150	0.5	1,200	6[c]

a: 2 morning, 2 evening
b: 2 morning, 3 evening
c: 3 morning, 3 evening

Duration of treatment
Predictability of sustained virological response: Patients infected with virus genotype 1 who fail to achieve virological response at Week 12 are highly unlikely to become sustained virological responders (see also section **5.1**).

- **Genotype 1**: For patients who exhibit virological response at week 12, treatment should be continued for another nine month period (i.e., a total of 48 weeks).
- **Genotypes 2 or 3**: It is recommended that all patients be treated for 24 weeks.
- **Genotype 4:** In general, patients infected with genotype 4 are considered harder to treat and limited study data (n=66) indicate they are compatible with a posology as for genotype 1.

PegIntron monotherapy
As monotherapy the PegIntron regimen is 0.5 or 1.0 microgram/kg/week. The lowest vial or pen strength available is 50 μg/0.5 ml; therefore for patients prescribed 0.5 μg/kg/week, doses must be adjusted by volume as shown in **Table 2**. For the 1.0 μg/kg dose, similar volume adjustments can be made or alternate vial strengths can be used as shown in **Table 2**.

Table 2- Monotherapy Dosing

	0.5 μg/kg		1.0 μg/kg	
Body Weight (kg)	Vial/Pen Strength (μg/0.5ml)	Administer Once Weekly (ml)	Vial/Pen Strength (μg/0.5ml)	Administer Once Weekly (ml)
30-35	50*	0.15	50	0.3
36-45	50*	0.2	50	0.4
46-56	50*	0.25	50	0.5
57-72	50	0.3	80	0.4
73-88	50	0.4	80	0.5

89-106	50	0.5	100	0.5
> 106**	80	0.4	120	0.5
* Must use vial. Minimum delivery for pen is 0.3 ml. ** For patients > 120 kg, use 80 µg/0.5 ml vial				

Duration of treatment
For patients who exhibit virological response at Week 12, treatment should be continued for at least another three-month period (i.e., a total of six months). The decision to extend therapy to one year of treatment should be based on prognostic factors (e.g., genotype, age > 40 years, male gender, bridging fibrosis).

Dose modification for all patients
If severe adverse reactions or laboratory abnormalities develop during treatment with PegIntron monotherapy or PegIntron in combination with ribavirin, modify the dosages of each product as appropriate, until the adverse reactions abate. Guidelines were developed in clinical trials for dose modification.

Combination Therapy Dose Reduction Guidelines

Table 2a Dose modification guidelines for combination therapy (with ribavirin)

Laboratory values	**Reduce only ribavirin dose to 600 mg/day* if:**	**Reduce only PegIntron dose to one-half dose if:**	**Discontinue combination therapy if:**
Haemoglobin	< 10 g/dl	-	< 8.5 g/dl
Haemoglobin in: Patients with history of stable cardiac disease	≥ 2 g/dl decrease in haemoglobin during any four week period during treatment (permanent dose reduction)		< 12 g/dl after four weeks of dose reduction
White blood cells	-	< 1.5 x 10^9/l	< 1.0 x 10^9/l
Neutrophils	-	< 0.75 x 10^9/l	< 0.5 x 10^9/l
Platelets	-	< 50 x 10^9/l	< 25 x 10^9/l
Bilirubin – direct	-	-	2.5 x ULN**
Bilirubin - indirect	> 5 mg/dl	-	> 4 mg/dl (for > 4 weeks)
Creatinine	-	-	> 2.0 mg/dl
ALT/AST	-	-	2 x baseline and > 10 x ULN**

* Patients whose dose of ribavirin is reduced to 600 mg daily receive one 200 mg capsule in the morning and two 200 mg capsules in the evening.

** Upper limit of normal

Dose reduction of PegIntron may be accomplished by either reducing the prescribed volume by one-half or by utilizing a lower dose strength as shown in **Table 2b**.

Table 2b – Reduced PegIntron Dosing for Combination Therapy

Body Weight (kg)	**Target Reduced Dose (µg)**	**Vial/Pen Strength (µg/0.5 ml)**	**Administer Once Weekly (ml)**	**Amount Delivered (µg)**
< 40	25	50*	0.25	25
40-50	32	50	0.3	30
51-64	40	50	0.4	40
65-75	50	50	0.5	50

76-85	60	80	0.4	64
> 85	75	100	0.4	80
*Must use vial. Minimum delivery for pen is 0.3 ml.				

PegIntron Monotherapy Dose Reduction Guidelines

Dose modification guidelines for patients who use PegIntron monotherapy are shown in **Table 3a.**

Table 3a Dose modification guidelines for PegIntron monotherapy		
Laboratory values	**Reduce PegIntron to one-half dose if:**	**Discontinue PegIntron if:**
Neutrophils	< 0.75 x 10^9/l	< 0.5 x 10^9/l
Platelets	< 50 x 10^9/l	< 25 x 10^9/l

Dose reduction for patients who use 0.5 µg/kg PegIntron monotherapy must be accomplished by reducing the prescribed volume by one-half. The 50 µg/0.5 ml vial must be used if necessary since the pen can only deliver a minimum volume of 0.3 ml.

For patients who use 1.0 µg/kg PegIntron monotherapy, dose reduction may be accomplished by reducing the prescribed volume by one-half or by utilizing a lower dose strength as shown in **Table 3b**.

Table 3b – Reduced PegIntron Dose for the 1.0 µg/kg Monotherapy Regimen				
Body Weight (kg)	**Target Reduced Dose (µg)**	**Vial/Pen Strength (µg/0.5ml)**	**Administer Once Weekly (ml)**	**Amount Delivered (µg)**
30-35	15	50*	0.15	15
36-45	20	50*	0.20	20
46-56	25	50*	0.25	25
57-72	32	50	0.3	30
73-89	40	50	0.4	40
90-106	50	50	0.5	50
> 106	60	80	0.4	64
*Must use vial. Minimum delivery for pen is 0.3 ml.				

Special populations

Use in renal impairment: The clearance of PegIntron is reduced in patients with significant renal impairment. Patients with creatinine clearance ≤ 50 ml/minute must not be treated with PegIntron (see section **5.2**). It is recommended that patients with moderate renal impairment be closely monitored and that their weekly dose of PegIntron be reduced if medically appropriate.

Use in hepatic impairment: The safety and efficacy of PegIntron therapy has not been evaluated in patients with severe hepatic dysfunction, therefore PegIntron must not be used for these patients.

Use in the elderly (≥ 65 years of age): There are no apparent age-related effects on the pharmacokinetics of PegIntron. Data from elderly patients treated with a single dose of PegIntron suggest no alteration in PegIntron dose is necessary based on age (see section **5.2**).

Use in patients under the age of 18 years: PegIntron is not recommended for use in children or adolescents under the age of 18, as there is no experience in this group.

4.3 Contraindications

- Hypersensitivity to the active substance or to any interferon or to any of the excipients;
- Pregnant women;
- Women who are breast-feeding;
- A history of severe pre-existing cardiac disease, including unstable or uncontrolled cardiac disease in the previous six months (see section **4.4**);
- Severe, debilitating medical conditions, including patients with chronic renal failure or creatinine clearance < 50 ml/minute;
- Autoimmune hepatitis or a history of autoimmune disease;
- Severe hepatic dysfunction or decompensated cirrhosis of the liver;
- Pre-existing thyroid disease unless it can be controlled with conventional treatment;
- Epilepsy and/or compromised central nervous system (CNS) function.

4.4 Special warnings and special precautions for use

There is no experience with PegIntron in combination with ribavirin in patients who have relapsed after interferon alpha + ribavirin therapy.

All patients in the chronic hepatitis C studies had a liver biopsy before inclusion, but in certain cases (i.e. patients with genotype 2 and 3), treatment may be possible without histological confirmation. Current treatment guidelines should be consulted as to whether a liver biopsy is needed prior to commencing treatment.

Acute hypersensitivity: Acute hypersensitivity reactions (e.g., urticaria, angioedema, bronchoconstriction, anaphylaxis) have been observed rarely during interferon alfa-2b therapy. If such a reaction develops during treatment with PegIntron, discontinue treatment and institute appropriate medical therapy immediately. Transient rashes do not necessitate interruption of treatment.

Cardiovascular system: As with interferon alfa-2b, patients with a history of congestive heart failure, myocardial infarction and/or previous or current arrhythmic disorders, receiving PegIntron therapy require close monitoring. It is recommended that patients who have pre-existing cardiac abnormalities have electrocardiograms taken prior to and during the course of treatment. Cardiac arrhythmias (primarily supraventricular) usually respond to conventional therapy but may require discontinuation of PegIntron therapy.

Psychiatric and Central Nervous System (CNS): If treatment with peginterferon alfa-2b is judged necessary in patients with existence or history of severe psychiatric conditions, this should only be initiated after having ensured appropriate individualised diagnostic and therapeutic management of the psychiatric condition.
Severe CNS effects, particularly depression, suicidal ideation and attempted suicide have been observed in some patients during PegIntron therapy. Other CNS effects including aggressive behaviour, confusion and alterations of mental status have been observed with alpha interferon. If patients develop psychiatric or CNS problems, including clinical depression, it is recommended that the patient be carefully monitored due to the potential seriousness of these undesirable effects. If symptoms persist or worsen, discontinue PegIntron therapy.
More significant obtundation and coma, including cases of encephalopathy, have been observed in some patients, usually elderly, treated at higher doses for oncology indications. While these effects are generally reversible, in a few patients full resolution took up to three weeks. Very rarely, seizures have occurred with high doses of interferon alpha.

Liver function: As with all interferons, discontinue treatment with PegIntron in patients who develop prolongation of coagulation markers which might indicate liver decompensation.

Fever: While fever may be associated with the flu-like syndrome reported commonly during interferon therapy, other causes of persistent fever must be ruled out.

Hydration: Adequate hydration must be maintained in patients undergoing PegIntron therapy since hypotension related to fluid depletion has been seen in some patients treated with alpha interferons. Fluid replacement may be necessary.

Pulmonary changes: Pulmonary infiltrates, pneumonitis, and pneumonia, occasionally resulting in fatality, have been observed rarely in interferon alpha treated patients. Any patient developing fever, cough, dyspnea or other respiratory symptoms must have a chest X-ray taken. If the chest X-ray shows pulmonary infiltrates or there is evidence of pulmonary function impairment, the patient is to be monitored closely, and, if appropriate, discontinue interferon alpha. Prompt discontinuation of interferon alpha administration and treatment with corticosteroids appear to be associated with resolution of pulmonary adverse events.

Autoimmune disease: The development of auto-antibodies and autoimmune disorders has been reported during treatment with alpha interferons. Patients predisposed to the development of autoimmune disorders may be at increased risk. Patients with signs or symptoms compatible with autoimmune disorders should be evaluated carefully, and the benefit-risk of continued interferon therapy should be reassessed (see also section **4.4 Thyroid changes** and **4.8**).

Ocular changes: Ophthalmologic disorders, including retinal haemorrhages, cotton wool spots, and retinal artery or vein obstruction have been reported in rare instances after treatment with alpha interferons (see section **4.8**). All patients should have a baseline eye examination. Any patient complaining of ocular symptoms, including loss of visual acuity or visual field must have a prompt and complete eye examination. Periodic visual examinations are recommended during PegIntron therapy, particularly in patients with disorders that may be associated with retinopathy, such as diabetes mellitus or hypertension. Discontinuation of PegIntron should be considered in patients who develop new or worsening ophthalmological disorders.

Thyroid changes: Infrequently, patients treated for chronic hepatitis C with interferon alpha have developed thyroid abnormalities, either hypothyroidism or hyperthyroidism. Determine thyroid stimulating hormone (TSH) levels if, during the course of therapy, a patient develops symptoms consistent with possible thyroid dysfunction. In the presence of thyroid dysfunction, PegIntron treatment may be continued if TSH levels can be maintained in the normal range by medication.

Metabolic disturbances: Hypertriglyceridemia and aggravation of hypertriglyceridemia, sometimes severe, have been observed. Monitoring of lipid levels is, therefore, recommended.

HCV/HIV Coinfection
Patients co-infected with HIV and receiving Highly Active Anti-Retroviral Therapy (HAART) may be at increased risk of developing lactic acidosis. Caution should be used when adding PegIntron and ribavirin to HAART therapy (see ribavirin SPC).
Co-infected patients with advanced cirrhosis receiving HAART may be at increased risk of hepatic decompensation and death. Adding treatment with alfa interferons alone or in combination with ribavirin may increase the risk in this patient subset.

Organ transplant recipients: The safety and efficacy of PegIntron alone or in combination with ribavirin for the treatment of hepatitis C in liver or other organ transplant recipients have not been studied. Preliminary data indicates that interferon alpha therapy may be associated with an increased rate of kidney graft rejection. Liver graft rejection has also been reported.

Other: Due to reports of interferon alpha exacerbating pre-existing psoriatic disease and sarcoidosis, use of PegIntron in patients with psoriasis or sarcoidosis is recommended only if the potential benefit justifies the potential risk.

Laboratory tests: Standard haematologic tests, blood chemistry and a test of thyroid function must be conducted in all patients prior to initiating therapy. Acceptable baseline values that may be considered as a guideline prior to initiation of PegIntron therapy are:

- Platelets ≥ 100,000/mm^3
- Neutrophil count ≥ 1,500/mm^3
- TSH level must be within normal limits

Laboratory evaluations are to be conducted at weeks 2 and 4 of therapy, and periodically thereafter as clinically appropriate.

4.5 Interaction with other medicinal products and other forms of interaction

Results of a single-dose study with PegIntron demonstrated no effect on the activity of cytochrome (CY) P1A2, CYP2C8/9, CYP2D6, and hepatic CYP3A4 or N-acetyl transferase. Caution should be advised in the interpretation of these results as the use of other forms of interferon alpha result in a 50 % reduction in the clearance and thus a doubling of plasma concentrations of theophylline, a substrate of CYP1A2.

No pharmacokinetic interactions were noted between PegIntron and ribavirin in a multiple-dose pharmacokinetic study.

4.6 Pregnancy and lactation

There are no adequate data on the use of interferon alfa-2b in pregnant women. Interferon alfa-2b has been shown to be abortifacient in primates. PegIntron is likely to also cause this effect. PegIntron should not be used during pregnancy (see section **5.3**).

PegIntron is recommended for use in fertile women only when they are using effective contraception during the treatment period.

Lactation: It is not known whether the components of this medicinal product are excreted in human milk. Because of the potential for adverse reactions in nursing infants, nursing must be discontinued prior to initiation of treatment.

Ribavirin is teratogenic and embryocidal and must not be used in pregnant women (see ribavirin SPC, **5.3**).

4.7 Effects on ability to drive and use machines

Patients who develop fatigue, somnolence or confusion during treatment with PegIntron are cautioned to avoid driving or operating machinery.

4.8 Undesirable effects

The safety of PegIntron is evaluated from data from two clinical trials: one with PegIntron monotherapy, one with PegIntron in combination with ribavirin. In both cases, patients were treated for one year.

Table 4 describes the regimens and patient exposure for one year of treatment in patients with no previous exposure to interferon (interferon-naïve patients). Because of a significant overlap in the pattern of undesirable effects with PegIntron monotherapy, groups of patients have been brought together in **Table 5** to show the pattern of reported effects for all monotherapy groups.

Table 4	Regimens and patient exposure	
Treatment	**Regimen**	**Number of patients treated for one year**
PegIntron + ribavirin	PegIntron (1.5 micrograms/kg/week) + ribavirin (> 10.6 mg/kg/day)	188
Interferon alfa-2b + ribavirin	Interferon alfa-2b (3 MIU three times a week) + ribavirin (1,000/1,200 mg/day)	505
PegIntron monotherapy	PegIntron (0.5 microgram/kg/week)	315
	PegIntron (1.0 microgram/kg/week)	297
	PegIntron (1.5 micrograms/kg/week)	304

Table 5 Undesirable effects reported in clinical trials (≥ 10 % of patients in PegIntron + ribavirin group)			
	PegIntron + ribavirin	**Interferon alfa-2b + ribavirin**	**PegIntron monotherapy**
Application site disorder			
Injection site inflammation	20 %	17 %	39-44 %
Injection site reaction	54 %	36 %	7-9 %
Body as a whole			
Headache	58 %	57 %	57-63 %
Fatigue	56 %	59 %	43 %
Rigors	42 %	40 %	33-43 %
Fever	39 %	32 %	29-43 %
Flu-like symptoms	21 %	23 %	18-25 %
Asthenia	28 %	17 %	12-14 %
Weight decrease	30 %	19 %	8-18 %
Gastrointestinal			
Nausea	43 %	31 %	20-23 %
Anorexia	35 %	26 %	10-25 %
Diarrhoea	20 %	13 %	14-17 %
Abdominal pain	12 %	9 %	11 %
Vomiting	16 %	10 %	4-7 %
Musculoskeletal			
Myalgia	49 %	49 %	46-60 %
Arthralgia	31 %	26 %	23-28 %
Musculoskeletal pain	15 %	11 %	11-13 %
Psychiatric			
Depression	34 %	32 %	26 %
Irritability	32 %	34 %	19 %
Insomnia	37 %	41 %	16-19 %
Anxiety	14 %	14 %	8 %
Concentration impaired	18 %	21 %	9-10 %
Emotional lability	11 %	10 %	5 %
Respiratory system			
Pharyngitis	10 %	7 %	3 %
Coughing	14 %	11 %	4 %
Dyspnea	26 %	22 %	5 %
Skin and appendages			
Alopecia	45 %	32 %	20-34 %
Pruritus	27 %	27 %	7-9 %
Skin dry	23 %	21 %	6-9 %
Rash	21 %	21 %	5-7 %
Other			
Dizziness	17 %	16 %	7-12 %
Infection viral	10 %	5 %	4-5 %
Mouth dry	10 %	8 %	4-8 %

Table 6 Undesirable effects reported in clinical trials (1%-< 10% of patients treated with PegIntron + ribavirin or PegIntron monotherapy)		
Body system	**5-10%**	**1-<5%**
Body as a whole	chest pain, RUQ pain, malaise	erythema, injection site pain, flushing, thirst, herpes simplex, face or peripheral oedema, dehydration
Cardiovascular		tachycardia, palpitation, hypotension, hypertension, syncope
Central/peripheral nervous system	paresthesia	hypoaesthesia, hyperaesthesia, hypertonia, decreased libido, confusion, tremor, vertigo, migraine, tinnitus, hearing impairment/loss, ataxia, neuralgia
Endocrine	hypothyroidism,	hyperthyroidism, amenorrhoea, prostatitis, hyperuricemia, hypocalcemia
Gastrointestinal	dyspepsia,	constipation, taste perversion, loose stools, stomatitis, ulcerative stomatitis, gingival bleeding, glossitis, flatulence, hemorrhoids, gastroesophageal reflux, hepatomegaly, bilirubinemia, gingivitis
Haematologic	anaemia, leukopaenia	thrombocytopenia, lymphadenopathy,
Musculoskeletal		arthritis
Ocular		blurred vision, conjunctivitis, lacrimal gland disorder, eye pain
Psychiatric	agitation, nervousness	aggressive behaviour, somnolence, behavior disorder, apathy, appetite increased, sleep disorder, dreaming abnormal
Reproductive	menstrual disorder, menorrhagia	ovarian disorder, vaginal disorder, sexual dysfunction (not specified), impotence, breast pain
Respiratory		nonproductive cough, rhinitis, sinusitis, bronchitis, respiratory disorder, nasal congestion, rhinorrhea, dysphonia, epistaxis
Resistance mechanism		otitis media, fungal infection, bacterial infection
Skin and appendages	increased sweating	erythematous rash, eczema, photosensitivity reaction, maculopapular rash, abnormal hair texture, acne, dermatitis, furunculosis, nail disorder, psoriasis, urticaria
Urinary		micturition frequency, urine abnormal

Most cases of neutropaenia and thrombocytopaenia were mild (WHO grades 1 or 2). There were some cases of more severe neutropenia in patients treated with the recommended doses of PegIntron in combination with ribavirin (WHO grade 3: 39 of 186 [21 %]; and WHO grade 4: 13 of 186 [7 %]).

In a clinical trial, approximately 1.2 % of patients treated with PegIntron or interferon alfa-2b in combination with ribavirin reported life-threatening psychiatric events during treatment. These events included suicidal ideation and attempted suicide (see section **4.4)**. Following marketing, psychosis and hallucination have been reported rarely.

Rarely reported events with interferon alfa-2b, including PegIntron, include seizure, pancreatitis, arrhythmia, peripheral neuropathy, diabetes, rhabdomyolysis, myositis, renal insufficiency and renal failure.

Cardiovascular (CVS) adverse events, particularly arrhythmia, appeared to be correlated mostly with pre-existing CVS disease and prior therapy with cardiotoxic agents (see section **4.4**). Cardiomyopathy, that may be reversible upon discontinuation of interferon alpha, has been reported rarely in patients without prior evidence of cardiac disease.

Very rarely cases of erythema multiforme, Stevens Johnson syndrome, toxic epidermal necrolysis, cardiac ischaemia, myocardial infarction, cerebrovascular ischaemia, cerebrovascular hemorrhage, encephalopathy, sarcoidosis or exacerbation of sarcoidosis, interstitial lung disease and injection site necrosis have been reported. Ulcerative and ischaemic colitis have been reported very rarely with PegIntron.

Very rarely, interferon alfa-2b or PegIntron used alone or in combination with ribavirin may be associated with aplastic anaemia.

Ophthalmological disorders that have been reported rarely with alpha interferons include retinopathies (including macular oedema), retinal haemorrhages, retinal artery or vein obstruction, cotton wool spots, loss of visual acuity or visual field, optic neuritis, and papilloedema (see section **4.4**).

A wide variety of autoimmune and immune-mediated disorders have been reported with alpha interferons including thyroid disorders, idiopathic and thrombotic thrombocytopenic purpura, vasculitis, neuropathies including mononeuropathies (see also section **4.4**, **Autoimmune disorders**).

4.9 Overdose

In clinical trials, cases of accidental overdose, at never more than twice the prescribed dose, were reported. There were no serious reactions. Undesirable effects resolved during continued administration of PegIntron.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunostimulants, Cytokines and immunomodulators, Interferons, Peginterferon alfa-2b, ATC code: L03A B10.

Recombinant interferon alfa-2b is covalently conjugated with monomethoxy polyethylene glycol at an average degree of substitution of 1 mole of polymer/mole of protein. The average molecular mass is approximately 31,300 daltons of which the protein moiety constitutes approximately 19,300.

Interferon alfa-2b
In vitro and *in vivo* studies suggest that the biological activity of PegIntron is derived from its interferon alfa-2b moiety.

Interferons exert their cellular activities by binding to specific membrane receptors on the cell surface. Studies with other interferons have demonstrated species specificity. However, certain monkey species, e.g., Rhesus monkeys, are susceptible to pharmacodynamic stimulation upon exposure to human type 1 interferons.

Once bound to the cell membrane, interferon initiates a complex sequence of intracellular events that include the induction of certain enzymes. It is thought that this process, at least in part, is responsible for the various cellular responses to interferon, including inhibition of virus replication in virus-infected cells, suppression of cell proliferation and such immunomodulating activities as enhancement

of the phagocytic activity of macrophages and augmentation of the specific cytotoxicity of lymphocytes for target cells. Any or all of these activities may contribute to interferon's therapeutic effects.

Recombinant interferon alfa-2b also inhibits viral replication *in vitro* and *in vivo*. Although the exact antiviral mode of action of recombinant interferon alfa-2b is unknown, it appears to alter the host cell metabolism. This action inhibits viral replication or if replication occurs, the progeny virions are unable to leave the cell.

PegIntron
PegIntron pharmacodynamics were assessed in a rising single-dose trial in healthy subjects by examining changes in oral temperature, concentrations of effector proteins such as serum neopterin and 2'5'-oligoadenylate synthetase (2'5'-OAS), as well as white cell and neutrophil counts. Subjects treated with PegIntron showed mild dose-related elevations in body temperature. Following single doses of PegIntron between 0.25 and 2.0 micrograms/kg/week, serum neopterin concentration was increased in a dose-related manner. Neutrophil and white cell count reductions at the end of week 4 correlated with the dose of PegIntron.

PegIntron clinical trials
Two pivotal trials have been conducted, one (C/I97-010) with PegIntron monotherapy; the other (C/I98-580) with PegIntron in combination with ribavirin. Eligible patients for these trials had chronic hepatitis C confirmed by a positive HCV-RNA polymerase chain reaction (PCR) assay (> 30 IU/ml), a liver biopsy consistent with a histological diagnosis of chronic hepatitis with no other cause for the chronic hepatitis, and abnormal serum ALT.

In the PegIntron monotherapy trial, a total of 916 naïve chronic hepatitis C patients were treated with PegIntron (0.5, 1.0 or 1.5 micrograms/kg/week) for one year with a follow-up period of six months. In addition, 303 patients received interferon alfa-2b (3 million International Units [MIU] three times a week as a comparator. This study showed that PegIntron was superior to interferon alfa-2b (**Table 7**).

In the PegIntron combination trial, 1,530 naïve patients were treated for one year with one of the following combination regimens:
- PegIntron (1.5 micrograms/kg/week) + ribavirin (800 mg/day), (n = 511).
- PegIntron (1.5 micrograms/kg/week for one month followed by 0.5 microgram/kg/week for 11 months) + ribavirin (1,000/1,200 mg/day), (n = 514).
- Interferon alfa-2b (3 MIU three times a week) + ribavirin (1,000/1,200 mg/day) (n = 505).

In this trial, the combination of PegIntron (1.5 micrograms/kg/week) and ribavirin was significantly more effective than the combination of interferon alfa-2b and ribavirin (**Table 7**), particularly in patients infected with Genotype 1 (**Table 8**). Sustained response was assessed by the response rate six months after the cessation of treatment.

HCV genotype and baseline virus load are prognostic factors which are known to affect response rates. However, response rates in this trial were shown to be dependent also on the dose of ribavirin administered in combination with PegIntron or interferon alfa-2b. In those patients that received > 10.6 mg/kg ribavirin (800 mg dose in typical 75 kg patient), regardless of genotype or viral load, response rates were significantly higher than in those patients that received ≤ 10.6 mg/kg ribavirin (**Table 8**), while response rates in patients that received > 13.2 mg/kg ribavirin were even higher.

Table 7 Sustained virological response (% patients HCV negative)

	PegIntron monotherapy				**PegIntron + ribavirin**		
Treatment regimen	**P 1.5**	**P 1.0**	**P 0.5**	**I**	**P 1.5/R**	**P 0.5/R**	**I/R**
Number of patients	304	297	315	303	511	514	505
Response at end of treatment	49 %	41 %	33 %	24 %	65 %	56 %	54 %

Sustained response	**23 %***	**25 %**	**18 %**	**12 %**	**54 %****	**47 %**	**47 %**

P 1.5 PegIntron 1.5 micrograms/kg
P 1.0 PegIntron 1.0 microgram/kg
P 0.5 PegIntron 0.5 microgram/kg
I Interferon alfa-2b 3 MIU
P 1.5/R PegIntron (1.5 micrograms/kg) + ribavirin (800 mg)
P 0.5/R PegIntron (1.5 to 0.5 microgram/kg) + ribavirin (1,000/1,200 mg)
I/R Interferon alfa-2b (3 MIU) + ribavirin (1,000/1,200 mg)
* $p < 0.001$ P 1.5 vs. I
** $p = 0.0143$ P 1.5/R vs. I/R

Table 8 Sustained response rates with PegIntron + ribavirin (by ribavirin dose , genotype and viral load)

HCV Genotype	**Rebetol dose (mg/kg)**	**P 1.5/R**	**P 0.5/R**	**I/R**
All Genotypes	**All**	**54 %**	**47 %**	**47 %**
	≤ 10.6	50 %	41 %	27 %
	> 10.6	61 %	48 %	47 %
Genotype 1	**All**	**42 %**	**34 %**	**33 %**
	≤ 10.6	38 %	25 %	20 %
	> 10.6	48 %	34 %	34 %
Genotype 1 ≤ 600,000 IU/ml	All	73 %	51 %	45 %
	≤ 10.6	74 %	25 %	33 %
	> 10.6	71 %	52 %	45 %
Genotype 1 > 600,000 IU/ml	All	30 %	27 %	29 %
	≤ 10.6	27 %	25 %	17 %
	> 10.6	37 %	27 %	29 %
Genotype 2/3	**All**	**82 %**	**80 %**	**79 %**
	≤ 10.6	79 %	73 %	50 %
	> 10.6	88 %	80 %	80 %

P 1.5/R PegIntron (1.5 micrograms/kg) + ribavirin (800 mg)
P 0.5/R PegIntron (1.5 to 0.5 microgram/kg) + ribavirin (1,000/1,200 mg)
I/R Interferon alfa-2b (3 MIU) + ribavirin (1,000/1,200 mg)

In the PegIntron monotherapy study, the Quality of Life was generally less affected by 0.5 microgram/kg of PegIntron than by either 1.0 microgram/kg of PegIntron once weekly or 3 MIU of interferon alfa-2b three times a week.

In a separate trial, 224 patients with genotype 2 or 3 received PegIntron, 1.5 microgram/kg subcutaneously, once weekly, in combination with ribavirin 800 mg –1,400 mg p.o. for 6 months (based on body weight, only three patients weighing > 105 kg, received the 1,400 mg dose, which has not yet been validated) (**Table 9**). Twenty-four % had bridging fibrosis or cirrhosis (Knodell 3/4).

Table 9. Virologic Response at End of Treatment, Sustained Virologic Response and Relapse by HCV Genotype and Viral Load*

	PegIntron 1.5 μg/kg Once Weekly Plus Rebetol 800-1400 mg/day		
	End of Treatment Response	Sustained Virologic Response	Relapse
All Subjects	94 % (211/224)	81 % (182/224)	12 % (27/224)
HCV 2	100 % (42/42)	93 % (39/42)	7 % (3/42)
≤ 600,000 IU/ml	100 % (20/20)	95 % (19/20)	5 % (1/20)
> 600,000	100 % (22/22)	91 % (20/22)	9 % (2/22)

IU/mL			
HCV 3	93 % (169/182)	79 % (143/182)	14 % (24/166)
≤ 600,000 IU/ml	93 % (92/99)	86 % (85/99)	8 % (7/91)
> 600,000 IU/ml	93 % (77/83)	70 % (58/83)	23 % (17/75)

* Any subject with an undetectable HCV-RNA level at the Follow-Up Week 12 visit and missing data at the Follow-Up Week 24 visit was considered a sustained responder. Any subject with missing data in and after the Follow-Up Week 12 window was considered to be a non-responder at Week 24 of follow-up.

The 6 month treatment duration in this trial was better tolerated than one year of treatment in the pivotal combination trial; for discontinuation 5 % vs. 14 %, for dose modification 18 % vs. 49 %.

Predictability of sustained virological response
Virological reponse by week 12, defined as a 2-log viral load decrease or undetectable levels of HCV RNA has been shown to be predictive for sustained response (**Table 10**).

Table 10 Predictability of sustained response by viral response at week 12 and genotype*

Treatment	Genotype	Viral response at week 12	Sustained response	Negative predictive value
PegIntron 1.5 + ribavirin (> 10.6 mg/kg) 48-week treatment	1	Yes 75 % (82/110)	71 % (58/82)	----
		No 25 % (28/110)	0 % (0/28)	100 %
PegIntron 1.5 + ribavirin 800-1,400 mg 24-week treatment	2 and 3	Yes 99 % (213/215)	83 % (177/213)	----
		No 1 % (2/215)	50 % (1/2)	50 %

* reflects patients with 12 week data available

The negative predictive value for sustained response in patients treated with PegIntron in monotherapy was 98 %.

5.2 Pharmacokinetic properties

PegIntron is a well characterized polyethylene glycol-modified (“pegylated”) derivative of interferon alfa-2b and is predominantly composed of monopegylated species. The plasma half-life of PegIntron is prolonged compared with non-pegylated interferon alfa-2b. PegIntron has a potential to depegylate to free interferon alfa-2b. The biologic activity of the pegylated isomers is qualitatively similar, but weaker than free interferon alfa-2b.

Following subcutaneous administration, maximal serum concentrations occur between 15-44 hours post-dose, and are sustained for up to 48-72 hours post-dose.

PegIntron C_{max} and AUC measurements increase in a dose-related manner. Mean apparent volume of distribution is 0.99 l/kg.

Upon multiple dosing, there is an accumulation of immunoreactive interferons. There is, however, only a modest increase in biologic activity as measured by a bioassay.

Mean (SD) PegIntron elimination half-life is approximately 40 hours (13.3 hours), with apparent clearance of 22.0 ml/hr·kg. The mechanisms involved in clearance of interferons in man have not yet been fully elucidated. However, renal elimination may account for a minority (approximately 30 %) of PegIntron apparent clearance.

Renal function: Renal clearance appears to account for 30 % of total clearance of PegIntron. In a single dose study (1.0 microgram/kg) in patients with impaired renal function, C_{max}, AUC, and half-life increased in relation to the degree of renal impairment.

Based on these data, no dose modification is recommended based on creatinine clearance. However, because of marked intra-subject variability in interferon pharmacokinetics, it is recommended that patients be monitored closely during treatment with PegIntron (see section **4.2**). Patients with severe renal dysfunction or creatinine clearance < 50 ml/min must not be treated with PegIntron.

Hepatic function: The pharmacokinetics of PegIntron have not been evaluated in patients with severe hepatic dysfunction.

Elderly patients ≥ 65 years of age: The pharmacokinetics of PegIntron following a single subcutaneous dose of 1.0 microgram/kg were not affected by age. The data suggest that no alteration in PegIntron dosage is necessary based on advancing age.

Patients under the age of 18 years: Specific pharmacokinetic evaluations have not been performed on these patients. PegIntron is indicated for the treatment of chronic hepatitis C only in patients 18 years of age or older.

Interferon neutralising factors: Interferon neutralising factor assays were performed on serum samples of patients who received PegIntron in the clinical trial. Interferon neutralising factors are antibodies which neutralise the antiviral activity of interferon. The clinical incidence of neutralising factors in patients who received PegIntron 0.5 micrograms/kg is 1.1 %.

5.3 Preclinical safety data

PegIntron: Adverse events not observed in clinical trials were not seen in toxicity studies in monkeys. These studies were limited to four weeks due to the appearance of anti-interferon antibodies in most monkeys.

Reproduction studies of PegIntron have not been performed. Interferon alfa-2b has been shown to be an abortifacient in primates. PegIntron is likely to also cause this effect. Effects on fertility have not been determined. PegIntron showed no genotoxic potential. (see section **4.6** for relevant human data. It is not known whether the components of this medicinal product are excreted in human milk. Therefore, nursing must be discontinued prior to the initiation of therapy.)

The relative non-toxicity of monomethoxy-polyethylene glycol (mPEG), which is liberated from PegIntron by metabolism *in vivo* has been demonstrated in preclinical acute and subchronic toxicity studies in rodents and monkeys, standard embryo-foetal development studies and in *in vitro* mutagenicity assays.

PegIntron plus ribavirin: When used in combination with ribavirin, PegIntron did not cause any effects not previously seen with either active substance alone. The major treatment-related change was a reversible, mild to moderate anaemia, the severity of which was greater than that produced by either active substance alone.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder for solution for injection:
Disodium phosphate, anhydrous,
Sodium dihydrogen phosphate dihydrate,
Sucrose,
Polysorbate 80.
Solvent for parenteral use:
Water for injections.

6.2 Incompatibilities

This medicinal product should only be reconstituted with the solvent provided and must not be mixed with other medicinal products (see also section **6.6**).

6.3 Shelf life

3 years

After reconstitution:
- Chemical and physical in-use stability has been demonstrated for 24 hours at 2°C - 8ºC.
- From a microbiological point of view, the product is to be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C - 8°C.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).

6.5 Nature and contents of container

The powder is contained in a 2 ml vial, Type I flint glass, with a butyl rubber stopper in an aluminium flip-off seal with a polypropylene bonnet. The solvent is presented in a 2 ml ampoule, Type I flint glass. PegIntron 120 micrograms is supplied as:
- 1 vial of powder for solution for injection and 1 ampoule of solvent for parenteral use;
- 1 vial of powder for solution for injection, 1 ampoule of solvent for parenteral use, 1 injection syringe, 2 injection needles and 1 cleansing swab;
- 4 vials of powder for solution for injection and 4 ampoules of solvent for parenteral use;
- 4 vials of powder for solution for injection, 4 ampoules of solvent for parenteral use, 4 injection syringes, 8 injection needles and 4 cleansing swabs;
- 6 vials of powder for solution for injection and 6 ampoules of solvent for parenteral use.
- 12 vials of powder for solution for injection, 12 ampoules of solvent for parenteral use, 12 injection syringes, 24 injection needles and 12 cleansing swabs.

Not all pack sizes may be marketed

6.6 Instructions for use and handling, and disposal

PegIntron is supplied as a powder of peginterferon alfa-2b at a strength of 120 micrograms for single use. Each vial must be reconstituted with 0.7 ml of water for injections for administration of up to 0.5 ml of solution. A small volume is lost during preparation of PegIntron for injection when the dose is measured and injected. Therefore, each vial contains an excess amount of solvent and PegIntron powder to ensure delivery of the labelled dose in 0.5 ml of PegIntron, solution for injection. The reconstituted solution has a concentration of 120 micrograms/0.5 ml.

Using a sterilised injection syringe and injection needle, inject 0.7 ml of water for injections into the vial of PegIntron. Agitate gently to complete dissolution of powder. The appropriate dose can then be withdrawn with a sterilised injection syringe and injected.

As for all parenteral medicinal products, inspect visually the reconstituted solution prior to administration. The reconstituted solution should be clear and colourless. Do not use if discolouration or particulate matter is present. Discard any unused material.

7. MARKETING AUTHORISATION HOLDER

SP Europe
73, rue de Stalle
B-1180 Bruxelles
Belgium

8. MARKETING AUTHORISATION NUMBERS

EU/1/00/131/016
EU/1/00/131/017
EU/1/00/131/018
EU/1/00/131/019
EU/1/00/131/020
EU/1/00/131/029

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

25 May 2000

10. DATE OF REVISION OF THE TEXT

1. NAME OF THE MEDICINAL PRODUCT

PegIntron 150 micrograms powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of PegIntron, powder for solution for injection contains 150 micrograms of peginterferon alfa-2b as measured on a protein basis.
Each vial provides 150 micrograms/0.5 ml of peginterferon alfa-2b when reconstituted as recommended.

The active substance is a covalent conjugate of recombinant interferon alfa-2b* with monomethoxy polyethylene glycol. The potency of this product should not be compared to that of another pegylated or non-pegylated protein of the same therapeutic class. For more information, see section **5.1.**
*produced by rDNA technology in *E.coli* cells harbouring a genetically engineered plasmid hybrid encompassing an interferon alfa-2b gene from human leukocytes

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection
The white powder is contained in a 2 ml glass vial and the clear and colourless solvent is presented in a 2 ml glass ampoule.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PegIntron is indicated for the treatment of adult patients with chronic hepatitis C who have elevated transaminases without liver decompensation and who are positive for serum HCV-RNA or anti-HCV (see section **4.4**).

The best way to use PegIntron in this indication is in combination with ribavirin.

This combination is indicated in naïve patients as well as in patients who have previously responded (with normalisation of ALT at the end of treatment) to interferon alpha monotherapy but who have subsequently relapsed.

Interferon monotherapy, including PegIntron, is indicated mainly in case of intolerance or contraindication to ribavirin.

Please refer also to the ribavirin Summary of Product Characteristics (SPC) when PegIntron is to be used in combination with ribavirin.

4.2 Posology and method of administration

Treatment should be initiated and monitored only by a physician experienced in the management of patients with hepatitis C.

Dose to be administered
PegIntron should be administered as a once weekly subcutaneous injection. The dose administered depends on whether it is used in combination with ribavirin or as monotherapy.

Combination therapy
PegIntron 1.5 micrograms/kg/week in combination with ribavirin capsules.

The intended dose of 1.5 μg/kg of PegIntron to be used in combination with ribavirin may be delivered in weight categories with the pen/vial strengths according to **Table 1**. Ribavirin capsules are to be administered orally each day in two divided doses with food (morning and evening).

Table 1 - Dosing for Combination Therapy

Body Weight (kg)	PegIntron		Ribavirin Capsules	
	Vial/Pen Strength (μg/0.5ml)	Administer Once Weekly (ml)	Total Daily Dose (mg)	Number of Capsules (200 mg)
< 40	50	0.5	800	4[a]
40-50	80	0.4	800	4[a]
51-64	80	0.5	800	4[a]
65-75	100	0.5	1,000	5[b]
76-85	120	0.5	1,000	5[b]
> 85	150	0.5	1,200	6[c]

a: 2 morning, 2 evening
b: 2 morning, 3 evening
c: 3 morning, 3 evening

Duration of treatment
Predictability of sustained virological response: Patients infected with virus genotype 1 who fail to achieve virological response at Week 12 are highly unlikely to become sustained virological responders (see also section **5.1**).

- **Genotype 1**: For patients who exhibit virological response at week 12, treatment should be continued for another nine month period (i.e., a total of 48 weeks).
- **Genotypes 2 or 3**: It is recommended that all patients be treated for 24 weeks.
- **Genotype 4:** In general, patients infected with genotype 4 are considered harder to treat and limited study data (n=66) indicate they are compatible with a posology as for genotype 1.

PegIntron monotherapy
As monotherapy the PegIntron regimen is 0.5 or 1.0 microgram/kg/week. The lowest vial or pen strength available is 50 μg/0.5 ml; therefore for patients prescribed 0.5 μg/kg/week, doses must be adjusted by volume as shown in **Table 2**. For the 1.0 μg/kg dose, similar volume adjustments can be made or alternate vial strengths can be used as shown in **Table 2**.

Table 2- Monotherapy Dosing

	0.5 μg/kg		1.0 μg/kg	
Body Weight (kg)	Vial/Pen Strength (μg/0.5ml)	Administer Once Weekly (ml)	Vial/Pen Strength (μg/0.5ml)	Administer Once Weekly (ml)
30-35	50*	0.15	50	0.3
36-45	50*	0.2	50	0.4
46-56	50*	0.25	50	0.5
57-72	50	0.3	80	0.4
73-88	50	0.4	80	0.5

89-106	50	0.5	100	0.5
> 106**	80	0.4	120	0.5
* Must use vial. Minimum delivery for pen is 0.3 ml. ** For patients > 120 kg, use 80 µg/0.5 ml vial				

Duration of treatment
For patients who exhibit virological response at Week 12, treatment should be continued for at least another three-month period (i.e., a total of six months). The decision to extend therapy to one year of treatment should be based on prognostic factors (e.g., genotype, age > 40 years, male gender, bridging fibrosis).

Dose modification for all patients
If severe adverse reactions or laboratory abnormalities develop during treatment with PegIntron monotherapy or PegIntron in combination with ribavirin, modify the dosages of each product as appropriate, until the adverse reactions abate. Guidelines were developed in clinical trials for dose modification.

Combination Therapy Dose Reduction Guidelines

Table 2a Dose modification guidelines for combination therapy (with ribavirin)

Laboratory values	**Reduce only ribavirin dose to 600 mg/day* if:**	**Reduce only PegIntron dose to one-half dose if:**	**Discontinue combination therapy if:**
Haemoglobin	< 10 g/dl	-	< 8.5 g/dl
Haemoglobin in: Patients with history of stable cardiac disease	≥ 2 g/dl decrease in haemoglobin during any four week period during treatment (permanent dose reduction)		< 12 g/dl after four weeks of dose reduction
White blood cells	-	< 1.5 x 10^9/l	< 1.0 x 10^9/l
Neutrophils	-	< 0.75 x 10^9/l	< 0.5 x 10^9/l
Platelets	-	< 50 x 10^9/l	< 25 x 10^9/l
Bilirubin – direct	-	-	2.5 x ULN**
Bilirubin - indirect	> 5 mg/dl	-	> 4 mg/dl (for > 4 weeks)
Creatinine	-	-	> 2.0 mg/dl
ALT/AST	-	-	2 x baseline and > 10 x ULN**

* Patients whose dose of ribavirin is reduced to 600 mg daily receive one 200 mg capsule in the morning and two 200 mg capsules in the evening.

** Upper limit of normal

Dose reduction of PegIntron may be accomplished by either reducing the prescribed volume by one-half or by utilizing a lower dose strength as shown in **Table 2b**.

Table 2b – Reduced PegIntron Dosing for Combination Therapy

Body Weight (kg)	**Target Reduced Dose (µg)**	**Vial/Pen Strength (µg/0.5 ml)**	**Administer Once Weekly (ml)**	**Amount Delivered (µg)**
< 40	25	50*	0.25	25
40-50	32	50	0.3	30
51-64	40	50	0.4	40
65-75	50	50	0.5	50

76-85	60	80	0.4	64
> 85	75	100	0.4	80
*Must use vial. Minimum delivery for pen is 0.3 ml.				

PegIntron Monotherapy Dose Reduction Guidelines

Dose modification guidelines for patients who use PegIntron monotherapy are shown in **Table 3a.**

Table 3a Dose modification guidelines for PegIntron monotherapy		
Laboratory values	**Reduce PegIntron to one-half dose if:**	**Discontinue PegIntron if:**
Neutrophils	< 0.75 x 10^9/l	< 0.5 x 10^9/l
Platelets	< 50 x 10^9/l	< 25 x 10^9/l

Dose reduction for patients who use 0.5 µg/kg PegIntron monotherapy must be accomplished by reducing the prescribed volume by one-half. The 50 µg/0.5 ml vial must be used if necessary since the pen can only deliver a minimum volume of 0.3 ml.

For patients who use 1.0 µg/kg PegIntron monotherapy, dose reduction may be accomplished by reducing the prescribed volume by one-half or by utilizing a lower dose strength as shown in **Table 3b**.

Table 3b – Reduced PegIntron Dose for the 1.0 µg/kg Monotherapy Regimen				
Body Weight (kg)	**Target Reduced Dose (µg)**	**Vial/Pen Strength (µg/0.5ml)**	**Administer Once Weekly (ml)**	**Amount Delivered (µg)**
30-35	15	50*	0.15	15
36-45	20	50*	0.20	20
46-56	25	50*	0.25	25
57-72	32	50	0.3	30
73-89	40	50	0.4	40
90-106	50	50	0.5	50
> 106	60	80	0.4	64
*Must use vial. Minimum delivery for pen is 0.3 ml.				

Special populations

Use in renal impairment: The clearance of PegIntron is reduced in patients with significant renal impairment. Patients with creatinine clearance ≤ 50 ml/minute must not be treated with PegIntron (see section **5.2**). It is recommended that patients with moderate renal impairment be closely monitored and that their weekly dose of PegIntron be reduced if medically appropriate.

Use in hepatic impairment: The safety and efficacy of PegIntron therapy has not been evaluated in patients with severe hepatic dysfunction, therefore PegIntron must not be used for these patients.

Use in the elderly (≥ 65 years of age): There are no apparent age-related effects on the pharmacokinetics of PegIntron. Data from elderly patients treated with a single dose of PegIntron suggest no alteration in PegIntron dose is necessary based on age (see section **5.2**).

Use in patients under the age of 18 years: PegIntron is not recommended for use in children or adolescents under the age of 18, as there is no experience in this group.

4.3 Contraindications

- Hypersensitivity to the active substance or to any interferon or to any of the excipients;
- Pregnant women;
- Women who are breast-feeding;
- A history of severe pre-existing cardiac disease, including unstable or uncontrolled cardiac disease in the previous six months (see section **4.4**);
- Severe, debilitating medical conditions, including patients with chronic renal failure or creatinine clearance < 50 ml/minute;
- Autoimmune hepatitis or a history of autoimmune disease;
- Severe hepatic dysfunction or decompensated cirrhosis of the liver;
- Pre-existing thyroid disease unless it can be controlled with conventional treatment;
- Epilepsy and/or compromised central nervous system (CNS) function.

4.4 Special warnings and special precautions for use

There is no experience with PegIntron in combination with ribavirin in patients who have relapsed after interferon alpha + ribavirin therapy.

All patients in the chronic hepatitis C studies had a liver biopsy before inclusion, but in certain cases (i.e. patients with genotype 2 and 3), treatment may be possible without histological confirmation. Current treatment guidelines should be consulted as to whether a liver biopsy is needed prior to commencing treatment.

Acute hypersensitivity: Acute hypersensitivity reactions (e.g., urticaria, angioedema, bronchoconstriction, anaphylaxis) have been observed rarely during interferon alfa-2b therapy. If such a reaction develops during treatment with PegIntron, discontinue treatment and institute appropriate medical therapy immediately. Transient rashes do not necessitate interruption of treatment.

Cardiovascular system: As with interferon alfa-2b, patients with a history of congestive heart failure, myocardial infarction and/or previous or current arrhythmic disorders, receiving PegIntron therapy require close monitoring. It is recommended that patients who have pre-existing cardiac abnormalities have electrocardiograms taken prior to and during the course of treatment. Cardiac arrhythmias (primarily supraventricular) usually respond to conventional therapy but may require discontinuation of PegIntron therapy.

Psychiatric and Central Nervous System (CNS): If treatment with peginterferon alfa-2b is judged necessary in patients with existence or history of severe psychiatric conditions, this should only be initiated after having ensured appropriate individualised diagnostic and therapeutic management of the psychiatric condition.
Severe CNS effects, particularly depression, suicidal ideation and attempted suicide have been observed in some patients during PegIntron therapy. Other CNS effects including aggressive behaviour, confusion and alterations of mental status have been observed with alpha interferon. If patients develop psychiatric or CNS problems, including clinical depression, it is recommended that the patient be carefully monitored due to the potential seriousness of these undesirable effects. If symptoms persist or worsen, discontinue PegIntron therapy.
More significant obtundation and coma, including cases of encephalopathy, have been observed in some patients, usually elderly, treated at higher doses for oncology indications. While these effects are generally reversible, in a few patients full resolution took up to three weeks. Very rarely, seizures have occurred with high doses of interferon alpha.

Liver function: As with all interferons, discontinue treatment with PegIntron in patients who develop prolongation of coagulation markers which might indicate liver decompensation.

Fever: While fever may be associated with the flu-like syndrome reported commonly during interferon therapy, other causes of persistent fever must be ruled out.

Hydration: Adequate hydration must be maintained in patients undergoing PegIntron therapy since hypotension related to fluid depletion has been seen in some patients treated with alpha interferons. Fluid replacement may be necessary.

Pulmonary changes: Pulmonary infiltrates, pneumonitis, and pneumonia, occasionally resulting in fatality, have been observed rarely in interferon alpha treated patients. Any patient developing fever, cough, dyspnea or other respiratory symptoms must have a chest X-ray taken. If the chest X-ray shows pulmonary infiltrates or there is evidence of pulmonary function impairment, the patient is to be monitored closely, and, if appropriate, discontinue interferon alpha. Prompt discontinuation of interferon alpha administration and treatment with corticosteroids appear to be associated with resolution of pulmonary adverse events.

Autoimmune disease: The development of auto-antibodies and autoimmune disorders has been reported during treatment with alpha interferons. Patients predisposed to the development of autoimmune disorders may be at increased risk. Patients with signs or symptoms compatible with autoimmune disorders should be evaluated carefully, and the benefit-risk of continued interferon therapy should be reassessed (see also section **4.4 Thyroid changes** and **4.8**).

Ocular changes: Ophthalmologic disorders, including retinal haemorrhages, cotton wool spots, and retinal artery or vein obstruction have been reported in rare instances after treatment with alpha interferons (see section **4.8**). All patients should have a baseline eye examination. Any patient complaining of ocular symptoms, including loss of visual acuity or visual field must have a prompt and complete eye examination. Periodic visual examinations are recommended during PegIntron therapy, particularly in patients with disorders that may be associated with retinopathy, such as diabetes mellitus or hypertension. Discontinuation of PegIntron should be considered in patients who develop new or worsening ophthalmological disorders.

Thyroid changes: Infrequently, patients treated for chronic hepatitis C with interferon alpha have developed thyroid abnormalities, either hypothyroidism or hyperthyroidism. Determine thyroid stimulating hormone (TSH) levels if, during the course of therapy, a patient develops symptoms consistent with possible thyroid dysfunction. In the presence of thyroid dysfunction, PegIntron treatment may be continued if TSH levels can be maintained in the normal range by medication.

Metabolic disturbances: Hypertriglyceridemia and aggravation of hypertriglyceridemia, sometimes severe, have been observed. Monitoring of lipid levels is, therefore, recommended.

HCV/HIV Coinfection
Patients co-infected with HIV and receiving Highly Active Anti-Retroviral Therapy (HAART) may be at increased risk of developing lactic acidosis. Caution should be used when adding PegIntron and ribavirin to HAART therapy (see ribavirin SPC).
Co-infected patients with advanced cirrhosis receiving HAART may be at increased risk of hepatic decompensation and death. Adding treatment with alfa interferons alone or in combination with ribavirin may increase the risk in this patient subset.

Organ transplant recipients: The safety and efficacy of PegIntron alone or in combination with ribavirin for the treatment of hepatitis C in liver or other organ transplant recipients have not been studied. Preliminary data indicates that interferon alpha therapy may be associated with an increased rate of kidney graft rejection. Liver graft rejection has also been reported.

Other: Due to reports of interferon alpha exacerbating pre-existing psoriatic disease and sarcoidosis, use of PegIntron in patients with psoriasis or sarcoidosis is recommended only if the potential benefit justifies the potential risk.

Laboratory tests: Standard haematologic tests, blood chemistry and a test of thyroid function must be conducted in all patients prior to initiating therapy. Acceptable baseline values that may be considered as a guideline prior to initiation of PegIntron therapy are:

- Platelets ≥ 100,000/mm^3
- Neutrophil count ≥ 1,500/mm^3
- TSH level must be within normal limits

Laboratory evaluations are to be conducted at weeks 2 and 4 of therapy, and periodically thereafter as clinically appropriate.

4.5 Interaction with other medicinal products and other forms of interaction

Results of a single-dose study with PegIntron demonstrated no effect on the activity of cytochrome (CY) P1A2, CYP2C8/9, CYP2D6, and hepatic CYP3A4 or N-acetyl transferase. Caution should be advised in the interpretation of these results as the use of other forms of interferon alpha result in a 50 % reduction in the clearance and thus a doubling of plasma concentrations of theophylline, a substrate of CYP1A2.

No pharmacokinetic interactions were noted between PegIntron and ribavirin in a multiple-dose pharmacokinetic study.

4.6 Pregnancy and lactation

There are no adequate data on the use of interferon alfa-2b in pregnant women. Interferon alfa-2b has been shown to be abortifacient in primates. PegIntron is likely to also cause this effect. PegIntron should not be used during pregnancy (see section **5.3**).

PegIntron is recommended for use in fertile women only when they are using effective contraception during the treatment period.

Lactation: It is not known whether the components of this medicinal product are excreted in human milk. Because of the potential for adverse reactions in nursing infants, nursing must be discontinued prior to initiation of treatment.

Ribavirin is teratogenic and embryocidal and must not be used in pregnant women (see ribavirin SPC, **5.3**).

4.7 Effects on ability to drive and use machines

Patients who develop fatigue, somnolence or confusion during treatment with PegIntron are cautioned to avoid driving or operating machinery.

4.8 Undesirable effects

The safety of PegIntron is evaluated from data from two clinical trials: one with PegIntron monotherapy, one with PegIntron in combination with ribavirin. In both cases, patients were treated for one year.

Table 4 describes the regimens and patient exposure for one year of treatment in patients with no previous exposure to interferon (interferon-naïve patients). Because of a significant overlap in the pattern of undesirable effects with PegIntron monotherapy, groups of patients have been brought together in **Table 5** to show the pattern of reported effects for all monotherapy groups.

Table 4	Regimens and patient exposure	
Treatment	**Regimen**	**Number of patients treated for one year**
PegIntron + ribavirin	PegIntron (1.5 micrograms/kg/week) + ribavirin (> 10.6 mg/kg/day)	188
Interferon alfa-2b + ribavirin	Interferon alfa-2b (3 MIU three times a week) + ribavirin (1,000/1,200 mg/day)	505
PegIntron monotherapy	PegIntron (0.5 microgram/kg/week)	315
	PegIntron (1.0 microgram/kg/week)	297
	PegIntron (1.5 micrograms/kg/week)	304

Table 5 Undesirable effects reported in clinical trials (≥ 10 % of patients in PegIntron + ribavirin group)			
	PegIntron + ribavirin	**Interferon alfa-2b + ribavirin**	**PegIntron monotherapy**
Application site disorder			
Injection site inflammation	20 %	17 %	39-44 %
Injection site reaction	54 %	36 %	7-9 %
Body as a whole			
Headache	58 %	57 %	57-63 %
Fatigue	56 %	59 %	43 %
Rigors	42 %	40 %	33-43 %
Fever	39 %	32 %	29-43 %
Flu-like symptoms	21 %	23 %	18-25 %
Asthenia	28 %	17 %	12-14 %
Weight decrease	30 %	19 %	8-18 %
Gastrointestinal			
Nausea	43 %	31 %	20-23 %
Anorexia	35 %	26 %	10-25 %
Diarrhoea	20 %	13 %	14-17 %
Abdominal pain	12 %	9 %	11 %
Vomiting	16 %	10 %	4-7 %
Musculoskeletal			
Myalgia	49 %	49 %	46-60 %
Arthralgia	31 %	26 %	23-28 %
Musculoskeletal pain	15 %	11 %	11-13 %
Psychiatric			
Depression	34 %	32 %	26 %
Irritability	32 %	34 %	19 %
Insomnia	37 %	41 %	16-19 %
Anxiety	14 %	14 %	8 %
Concentration impaired	18 %	21 %	9-10 %
Emotional lability	11 %	10 %	5 %
Respiratory system			
Pharyngitis	10 %	7 %	3 %
Coughing	14 %	11 %	4 %
Dyspnea	26 %	22 %	5 %
Skin and appendages			
Alopecia	45 %	32 %	20-34 %
Pruritus	27 %	27 %	7-9 %
Skin dry	23 %	21 %	6-9 %
Rash	21 %	21 %	5-7 %
Other			
Dizziness	17 %	16 %	7-12 %
Infection viral	10 %	5 %	4-5 %
Mouth dry	10 %	8 %	4-8 %

Table 6 Undesirable effects reported in clinical trials (1%-< 10% of patients treated with PegIntron + ribavirin or PegIntron monotherapy)		
Body system	**5-10%**	**1-<5%**
Body as a whole	chest pain, RUQ pain, malaise	erythema, injection site pain, flushing, thirst, herpes simplex, face or peripheral oedema, dehydration
Cardiovascular		tachycardia, palpitation, hypotension, hypertension, syncope
Central/peripheral nervous system	paresthesia	hypoaesthesia, hyperaesthesia, hypertonia, decreased libido, confusion, tremor, vertigo, migraine, tinnitus, hearing impairment/loss, ataxia, neuralgia
Endocrine	hypothyroidism,	hyperthyroidism, amenorrhoea, prostatitis, hyperuricemia, hypocalcemia
Gastrointestinal	dyspepsia,	constipation, taste perversion, loose stools, stomatitis, ulcerative stomatitis, gingival bleeding, glossitis, flatulence, hemorrhoids, gastroesophageal reflux, hepatomegaly, bilirubinemia, gingivitis
Haematologic	anaemia, leukopaenia	thrombocytopenia, lymphadenopathy,
Musculoskeletal		arthritis
Ocular		blurred vision, conjunctivitis, lacrimal gland disorder, eye pain
Psychiatric	agitation, nervousness	aggressive behaviour, somnolence, behavior disorder, apathy, appetite increased, sleep disorder, dreaming abnormal
Reproductive	menstrual disorder, menorrhagia	ovarian disorder, vaginal disorder, sexual dysfunction (not specified), impotence, breast pain
Respiratory		nonproductive cough, rhinitis, sinusitis, bronchitis, respiratory disorder, nasal congestion, rhinorrhea, dysphonia, epistaxis
Resistance mechanism		otitis media, fungal infection, bacterial infection
Skin and appendages	increased sweating	erythematous rash, eczema, photosensitivity reaction, maculopapular rash, abnormal hair texture, acne, dermatitis, furunculosis, nail disorder, psoriasis, urticaria
Urinary		micturition frequency, urine abnormal

Most cases of neutropaenia and thrombocytopaenia were mild (WHO grades 1 or 2). There were some cases of more severe neutropenia in patients treated with the recommended doses of PegIntron in combination with ribavirin (WHO grade 3: 39 of 186 [21 %]; and WHO grade 4: 13 of 186 [7 %]).

In a clinical trial, approximately 1.2 % of patients treated with PegIntron or interferon alfa-2b in combination with ribavirin reported life-threatening psychiatric events during treatment. These events included suicidal ideation and attempted suicide (see section **4.4)**. Following marketing, psychosis and hallucination have been reported rarely.

Rarely reported events with interferon alfa-2b, including PegIntron, include seizure, pancreatitis, arrhythmia, peripheral neuropathy, diabetes, rhabdomyolysis, myositis, renal insufficiency and renal failure.

Cardiovascular (CVS) adverse events, particularly arrhythmia, appeared to be correlated mostly with pre-existing CVS disease and prior therapy with cardiotoxic agents (see section **4.4**). Cardiomyopathy, that may be reversible upon discontinuation of interferon alpha, has been reported rarely in patients without prior evidence of cardiac disease.

Very rarely cases of erythema multiforme, Stevens Johnson syndrome, toxic epidermal necrolysis, cardiac ischaemia, myocardial infarction, cerebrovascular ischaemia, cerebrovascular hemorrhage, encephalopathy, sarcoidosis or exacerbation of sarcoidosis, interstitial lung disease and injection site necrosis have been reported. Ulcerative and ischaemic colitis have been reported very rarely with PegIntron.

Very rarely, interferon alfa-2b or PegIntron used alone or in combination with ribavirin may be associated with aplastic anaemia.

Ophthalmological disorders that have been reported rarely with alpha interferons include retinopathies (including macular oedema), retinal haemorrhages, retinal artery or vein obstruction, cotton wool spots, loss of visual acuity or visual field, optic neuritis, and papilloedema (see section **4.4**).

A wide variety of autoimmune and immune-mediated disorders have been reported with alpha interferons including thyroid disorders, idiopathic and thrombotic thrombocytopenic purpura, vasculitis, neuropathies including mononeuropathies (see also section **4.4**, **Autoimmune disorders**).

4.9 Overdose

In clinical trials, cases of accidental overdose, at never more than twice the prescribed dose, were reported. There were no serious reactions. Undesirable effects resolved during continued administration of PegIntron.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunostimulants, Cytokines and immunomodulators, Interferons, Peginterferon alfa-2b, ATC code: L03A B10.

Recombinant interferon alfa-2b is covalently conjugated with monomethoxy polyethylene glycol at an average degree of substitution of 1 mole of polymer/mole of protein. The average molecular mass is approximately 31,300 daltons of which the protein moiety constitutes approximately 19,300.

Interferon alfa-2b
In vitro and *in vivo* studies suggest that the biological activity of PegIntron is derived from its interferon alfa-2b moiety.

Interferons exert their cellular activities by binding to specific membrane receptors on the cell surface. Studies with other interferons have demonstrated species specificity. However, certain monkey species, e.g., Rhesus monkeys, are susceptible to pharmacodynamic stimulation upon exposure to human type 1 interferons.

Once bound to the cell membrane, interferon initiates a complex sequence of intracellular events that include the induction of certain enzymes. It is thought that this process, at least in part, is responsible for the various cellular responses to interferon, including inhibition of virus replication in virus-infected cells, suppression of cell proliferation and such immunomodulating activities as enhancement

of the phagocytic activity of macrophages and augmentation of the specific cytotoxicity of lymphocytes for target cells. Any or all of these activities may contribute to interferon's therapeutic effects.

Recombinant interferon alfa-2b also inhibits viral replication *in vitro* and *in vivo*. Although the exact antiviral mode of action of recombinant interferon alfa-2b is unknown, it appears to alter the host cell metabolism. This action inhibits viral replication or if replication occurs, the progeny virions are unable to leave the cell.

PegIntron
PegIntron pharmacodynamics were assessed in a rising single-dose trial in healthy subjects by examining changes in oral temperature, concentrations of effector proteins such as serum neopterin and 2'5'-oligoadenylate synthetase (2'5'-OAS), as well as white cell and neutrophil counts. Subjects treated with PegIntron showed mild dose-related elevations in body temperature. Following single doses of PegIntron between 0.25 and 2.0 micrograms/kg/week, serum neopterin concentration was increased in a dose-related manner. Neutrophil and white cell count reductions at the end of week 4 correlated with the dose of PegIntron.

PegIntron clinical trials
Two pivotal trials have been conducted, one (C/I97-010) with PegIntron monotherapy; the other (C/I98-580) with PegIntron in combination with ribavirin. Eligible patients for these trials had chronic hepatitis C confirmed by a positive HCV-RNA polymerase chain reaction (PCR) assay (> 30 IU/ml), a liver biopsy consistent with a histological diagnosis of chronic hepatitis with no other cause for the chronic hepatitis, and abnormal serum ALT.

In the PegIntron monotherapy trial, a total of 916 naïve chronic hepatitis C patients were treated with PegIntron (0.5, 1.0 or 1.5 micrograms/kg/week) for one year with a follow-up period of six months. In addition, 303 patients received interferon alfa-2b (3 million International Units [MIU] three times a week as a comparator. This study showed that PegIntron was superior to interferon alfa-2b (**Table 7**).

In the PegIntron combination trial, 1,530 naïve patients were treated for one year with one of the following combination regimens:
- PegIntron (1.5 micrograms/kg/week) + ribavirin (800 mg/day), (n = 511).
- PegIntron (1.5 micrograms/kg/week for one month followed by 0.5 microgram/kg/week for 11 months) + ribavirin (1,000/1,200 mg/day), (n = 514).
- Interferon alfa-2b (3 MIU three times a week) + ribavirin (1,000/1,200 mg/day) (n = 505).

In this trial, the combination of PegIntron (1.5 micrograms/kg/week) and ribavirin was significantly more effective than the combination of interferon alfa-2b and ribavirin (**Table 7**), particularly in patients infected with Genotype 1 (**Table 8**). Sustained response was assessed by the response rate six months after the cessation of treatment.

HCV genotype and baseline virus load are prognostic factors which are known to affect response rates. However, response rates in this trial were shown to be dependent also on the dose of ribavirin administered in combination with PegIntron or interferon alfa-2b. In those patients that received > 10.6 mg/kg ribavirin (800 mg dose in typical 75 kg patient), regardless of genotype or viral load, response rates were significantly higher than in those patients that received ≤ 10.6 mg/kg ribavirin (**Table 8**), while response rates in patients that received > 13.2 mg/kg ribavirin were even higher.

Table 7 Sustained virological response (% patients HCV negative)

	PegIntron monotherapy				**PegIntron + ribavirin**		
Treatment regimen	**P 1.5**	**P 1.0**	**P 0.5**	**I**	**P 1.5/R**	**P 0.5/R**	**I/R**
Number of patients	304	297	315	303	511	514	505
Response at end of treatment	49 %	41 %	33 %	24 %	65 %	56 %	54 %

Sustained response	**23 %***	**25 %**	**18 %**	**12 %**	**54 %****	**47 %**	**47 %**

P 1.5 PegIntron 1.5 micrograms/kg
P 1.0 PegIntron 1.0 microgram/kg
P 0.5 PegIntron 0.5 microgram/kg
I Interferon alfa-2b 3 MIU
P 1.5/R PegIntron (1.5 micrograms/kg) + ribavirin (800 mg)
P 0.5/R PegIntron (1.5 to 0.5 microgram/kg) + ribavirin (1,000/1,200 mg)
I/R Interferon alfa-2b (3 MIU) + ribavirin (1,000/1,200 mg)
* $p < 0.001$ P 1.5 vs. I
** $p = 0.0143$ P 1.5/R vs. I/R

Table 8 Sustained response rates with PegIntron + ribavirin (by ribavirin dose , genotype and viral load)

HCV Genotype	**Rebetol dose (mg/kg)**	**P 1.5/R**	**P 0.5/R**	**I/R**
All Genotypes	**All**	**54 %**	**47 %**	**47 %**
	≤ 10.6	50 %	41 %	27 %
	> 10.6	61 %	48 %	47 %
Genotype 1	**All**	**42 %**	**34 %**	**33 %**
	≤ 10.6	38 %	25 %	20 %
	> 10.6	48 %	34 %	34 %
Genotype 1 ≤ 600,000 IU/ml	All	73 %	51 %	45 %
	≤ 10.6	74 %	25 %	33 %
	> 10.6	71 %	52 %	45 %
Genotype 1 > 600,000 IU/ml	All	30 %	27 %	29 %
	≤ 10.6	27 %	25 %	17 %
	> 10.6	37 %	27 %	29 %
Genotype 2/3	**All**	**82 %**	**80 %**	**79 %**
	≤ 10.6	79 %	73 %	50 %
	> 10.6	88 %	80 %	80 %

P 1.5/R PegIntron (1.5 micrograms/kg) + ribavirin (800 mg)
P 0.5/R PegIntron (1.5 to 0.5 microgram/kg) + ribavirin (1,000/1,200 mg)
I/R Interferon alfa-2b (3 MIU) + ribavirin (1,000/1,200 mg)

In the PegIntron monotherapy study, the Quality of Life was generally less affected by 0.5 microgram/kg of PegIntron than by either 1.0 microgram/kg of PegIntron once weekly or 3 MIU of interferon alfa-2b three times a week.

In a separate trial, 224 patients with genotype 2 or 3 received PegIntron, 1.5 microgram/kg subcutaneously, once weekly, in combination with ribavirin 800 mg –1,400 mg p.o. for 6 months (based on body weight, only three patients weighing > 105 kg, received the 1,400 mg dose, which has not yet been validated) (**Table 9**). Twenty-four % had bridging fibrosis or cirrhosis (Knodell 3/4).

Table 9. Virologic Response at End of Treatment, Sustained Virologic Response and Relapse by HCV Genotype and Viral Load*

	PegIntron 1.5 μg/kg Once Weekly Plus Rebetol 800-1400 mg/day		
	End of Treatment Response	Sustained Virologic Response	Relapse
All Subjects	94 % (211/224)	81 % (182/224)	12 % (27/224)
HCV 2	100 % (42/42)	93 % (39/42)	7 % (3/42)
≤ 600,000 IU/ml	100 % (20/20)	95 % (19/20)	5 % (1/20)
> 600,000	100 % (22/22)	91 % (20/22)	9 % (2/22)

IU/mL			
HCV 3	93 % (169/182)	79 % (143/182)	14 % (24/166)
≤ 600,000 IU/ml	93 % (92/99)	86 % (85/99)	8 % (7/91)
> 600,000 IU/ml	93 % (77/83)	70 % (58/83)	23 % (17/75)

* Any subject with an undetectable HCV-RNA level at the Follow-Up Week 12 visit and missing data at the Follow-Up Week 24 visit was considered a sustained responder. Any subject with missing data in and after the Follow-Up Week 12 window was considered to be a non-responder at Week 24 of follow-up.

The 6 month treatment duration in this trial was better tolerated than one year of treatment in the pivotal combination trial; for discontinuation 5 % vs. 14 %, for dose modification 18 % vs. 49 %.

Predictability of sustained virological response
Virological reponse by week 12, defined as a 2-log viral load decrease or undetectable levels of HCV RNA has been shown to be predictive for sustained response (**Table 10**).

Table 10 Predictability of sustained response by viral response at week 12 and genotype*

Treatment	Genotype	Viral response at week 12	Sustained response	Negative predictive value
PegIntron 1.5 + ribavirin (> 10.6 mg/kg) 48-week treatment	1	Yes 75 % (82/110)	71 % (58/82)	----
		No 25 % (28/110)	0 % (0/28)	100 %
PegIntron 1.5 + ribavirin 800-1,400 mg 24-week treatment	2 and 3	Yes 99 % (213/215)	83 % (177/213)	----
		No 1 % (2/215)	50 % (1/2)	50 %

* reflects patients with 12 week data available

The negative predictive value for sustained response in patients treated with PegIntron in monotherapy was 98 %.

5.2 Pharmacokinetic properties

PegIntron is a well characterized polyethylene glycol-modified (“pegylated”) derivative of interferon alfa-2b and is predominantly composed of monopegylated species. The plasma half-life of PegIntron is prolonged compared with non-pegylated interferon alfa-2b. PegIntron has a potential to depegylate to free interferon alfa-2b. The biologic activity of the pegylated isomers is qualitatively similar, but weaker than free interferon alfa-2b.

Following subcutaneous administration, maximal serum concentrations occur between 15-44 hours post-dose, and are sustained for up to 48-72 hours post-dose.

PegIntron C_{max} and AUC measurements increase in a dose-related manner. Mean apparent volume of distribution is 0.99 l/kg.

Upon multiple dosing, there is an accumulation of immunoreactive interferons. There is, however, only a modest increase in biologic activity as measured by a bioassay.

Mean (SD) PegIntron elimination half-life is approximately 40 hours (13.3 hours), with apparent clearance of 22.0 ml/hr·kg. The mechanisms involved in clearance of interferons in man have not yet been fully elucidated. However, renal elimination may account for a minority (approximately 30 %) of PegIntron apparent clearance.

Renal function: Renal clearance appears to account for 30 % of total clearance of PegIntron. In a single dose study (1.0 microgram/kg) in patients with impaired renal function, C_{max}, AUC, and half-life increased in relation to the degree of renal impairment.

Based on these data, no dose modification is recommended based on creatinine clearance. However, because of marked intra-subject variability in interferon pharmacokinetics, it is recommended that patients be monitored closely during treatment with PegIntron (see section **4.2**). Patients with severe renal dysfunction or creatinine clearance < 50 ml/min must not be treated with PegIntron.

Hepatic function: The pharmacokinetics of PegIntron have not been evaluated in patients with severe hepatic dysfunction.

Elderly patients ≥ 65 years of age: The pharmacokinetics of PegIntron following a single subcutaneous dose of 1.0 microgram/kg were not affected by age. The data suggest that no alteration in PegIntron dosage is necessary based on advancing age.

Patients under the age of 18 years: Specific pharmacokinetic evaluations have not been performed on these patients. PegIntron is indicated for the treatment of chronic hepatitis C only in patients 18 years of age or older.

Interferon neutralising factors: Interferon neutralising factor assays were performed on serum samples of patients who received PegIntron in the clinical trial. Interferon neutralising factors are antibodies which neutralise the antiviral activity of interferon. The clinical incidence of neutralising factors in patients who received PegIntron 0.5 micrograms/kg is 1.1 %.

5.3 Preclinical safety data

PegIntron: Adverse events not observed in clinical trials were not seen in toxicity studies in monkeys. These studies were limited to four weeks due to the appearance of anti-interferon antibodies in most monkeys.

Reproduction studies of PegIntron have not been performed. Interferon alfa-2b has been shown to be an abortifacient in primates. PegIntron is likely to also cause this effect. Effects on fertility have not been determined. PegIntron showed no genotoxic potential. (see section **4.6** for relevant human data. It is not known whether the components of this medicinal product are excreted in human milk. Therefore, nursing must be discontinued prior to the initiation of therapy.)

The relative non-toxicity of monomethoxy-polyethylene glycol (mPEG), which is liberated from PegIntron by metabolism *in vivo* has been demonstrated in preclinical acute and subchronic toxicity studies in rodents and monkeys, standard embryo-foetal development studies and in *in vitro* mutagenicity assays.

PegIntron plus ribavirin: When used in combination with ribavirin, PegIntron did not cause any effects not previously seen with either active substance alone. The major treatment-related change was a reversible, mild to moderate anaemia, the severity of which was greater than that produced by either active substance alone.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder for solution for injection:
Disodium phosphate, anhydrous,
Sodium dihydrogen phosphate dihydrate,
Sucrose,
Polysorbate 80.
Solvent for parenteral use:
Water for injections.

6.2 Incompatibilities

This medicinal product should only be reconstituted with the solvent provided and must not be mixed with other medicinal products (see also section **6.6**).

6.3 Shelf life

3 years

After reconstitution:
- Chemical and physical in-use stability has been demonstrated for 24 hours at 2°C - 8ºC.
- From a microbiological point of view, the product is to be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C - 8°C.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).

6.5 Nature and contents of container

The powder is contained in a 2 ml vial, Type I flint glass, with a butyl rubber stopper in an aluminium flip-off seal with a polypropylene bonnet. The solvent is presented in a 2 ml ampoule, Type I flint glass. PegIntron 150 micrograms is supplied as:
- 1 vial of powder for solution for injection and 1 ampoule of solvent for parenteral use;
- 1 vial of powder for solution for injection, 1 ampoule of solvent for parenteral use, 1 injection syringe, 2 injection needles and 1 cleansing swab;
- 4 vials of powder for solution for injection and 4 ampoules of solvent for parenteral use;
- 4 vials of powder for solution for injection, 4 ampoules of solvent for parenteral use, 4 injection syringes, 8 injection needles and 4 cleansing swabs;
- 6 vials of powder for solution for injection and 6 ampoules of solvent for parenteral use.
- 12 vials of powder for solution for injection, 12 ampoules of solvent for parenteral use, 12 injection syringes, 24 injection needles and 12 cleansing swabs.

Not all pack sizes may be marketed

6.6 Instructions for use and handling, and disposal

PegIntron is supplied as a powder of peginterferon alfa-2b at a strength of 150 micrograms for single use. Each vial must be reconstituted with 0.7 ml of water for injections for administration of up to 0.5 ml of solution. A small volume is lost during preparation of PegIntron for injection when the dose is measured and injected. Therefore, each vial contains an excess amount of solvent and PegIntron powder to ensure delivery of the labelled dose in 0.5 ml of PegIntron, solution for injection. The reconstituted solution has a concentration of 150 micrograms/0.5 ml.

Using a sterilised injection syringe and injection needle, inject 0.7 ml of water for injections into the vial of PegIntron. Agitate gently to complete dissolution of powder. The appropriate dose can then be withdrawn with a sterilised injection syringe and injected.

As for all parenteral medicinal products, inspect visually the reconstituted solution prior to administration. The reconstituted solution should be clear and colourless. Do not use if discolouration or particulate matter is present. Discard any unused material.

7. MARKETING AUTHORISATION HOLDER

SP Europe
73, rue de Stalle
B-1180 Bruxelles
Belgium

8. MARKETING AUTHORISATION NUMBERS

EU/1/00/131/021
EU/1/00/131/022
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9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

25 May 2000

10. DATE OF REVISION OF THE TEXT

1. NAME OF THE MEDICINAL PRODUCT

PegIntron 50 micrograms, powder and solvent for solution for injection in pre-filled pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled pen of PegIntron 50 micrograms contains a sufficient amount of peginterferon alfa-2b as measured on a protein basis in a powder for solution for injection, and the corresponding amount of solvent, to provide 50 micrograms in 0.5 ml of peginterferon alfa-2b when reconstituted as recommended.

The active substance is a covalent conjugate of recombinant interferon alfa-2b* with monomethoxy polyethylene glycol. The potency of this product should not be compared to that of another pegylated or non-pegylated protein of the same therapeutic class. For more information, see section **5.1.**
*produced by rDNA technology in *E.coli* cells harbouring a genetically engineered plasmid hybrid encompassing an interferon alfa-2b gene from human leukocytes

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection
The white powder and the clear and colourless solvent are both contained in a two-chamber glass cartidge assembled into a single use pre-filled pen.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PegIntron is indicated for the treatment of adult patients with chronic hepatitis C who have elevated transaminases without liver decompensation and who are positive for serum HCV-RNA or anti-HCV (see section **4.4**).

The best way to use PegIntron in this indication is in combination with ribavirin.

This combination is indicated in naïve patients as well as in patients who have previously responded (with normalisation of ALT at the end of treatment) to interferon alpha monotherapy but who have subsequently relapsed.

Interferon monotherapy, including PegIntron, is indicated mainly in case of intolerance or contraindication to ribavirin.

Please refer also to the ribavirin Summary of Product Characteristics (SPC) when PegIntron is to be used in combination with ribavirin.

4.2 Posology and method of administration

Treatment should be initiated and monitored only by a physician experienced in the management of patients with hepatitis C.

Dose to be administered
PegIntron should be administered as a once weekly subcutaneous injection. The dose administered depends on whether it is used in combination with ribavirin or as monotherapy.

Combination therapy

PegIntron 1.5 micrograms/kg/week in combination with ribavirin capsules.

The intended dose of 1.5 μg/kg of PegIntron to be used in combination with ribavirin may be delivered in weight categories with the pen/vial strengths according to **Table 1**. Ribavirin capsules are to be administered orally each day in two divided doses with food (morning and evening).

Table 1 - Dosing for Combination Therapy

Body Weight (kg)	**PegIntron**		**Ribavirin Capsules**	
	Vial/Pen Strength (μg/0.5ml)	**Administer Once Weekly (ml)**	**Total Daily Dose (mg)**	**Number of Capsules (200 mg)**
< 40	50	0.5	800	4[a]
40-50	80	0.4	800	4[a]
51-64	80	0.5	800	4[a]
65-75	100	0.5	1,000	5[b]
76-85	120	0.5	1,000	5[b]
> 85	150	0.5	1,200	6[c]

a: 2 morning, 2 evening
b: 2 morning, 3 evening
c: 3 morning, 3 evening

Duration of treatment
Predictability of sustained virological response: Patients infected with virus genotype 1 who fail to achieve virological response at Week 12 are highly unlikely to become sustained virological responders (see also section **5.1**).

- **Genotype 1**: For patients who exhibit virological response at week 12, treatment should be continued for another nine month period (i.e., a total of 48 weeks).
- **Genotypes 2 or 3**: It is recommended that all patients be treated for 24 weeks.
- **Genotype 4:** In general, patients infected with genotype 4 are considered harder to treat and limited study data (n=66) indicate they are compatible with a posology as for genotype 1.

PegIntron monotherapy
As monotherapy the PegIntron regimen is 0.5 or 1.0 microgram/kg/week. The lowest vial or pen strength available is 50 μg/0.5 ml; therefore for patients prescribed 0.5 μg/kg/week, doses must be adjusted by volume as shown in **Table 2**. For the 1.0 μg/kg dose, similar volume adjustments can be made or alternate vial strengths can be used as shown in **Table 2**.

Table 2- Monotherapy Dosing

	0.5 μg/kg		**1.0 μg/kg**	
Body Weight (kg)	**Vial/Pen Strength (μg/0.5ml)**	**Administer Once Weekly (ml)**	**Vial/Pen Strength (μg/0.5ml)**	**Administer Once Weekly (ml)**
30-35	50*	0.15	50	0.3
36-45	50*	0.2	50	0.4
46-56	50*	0.25	50	0.5
57-72	50	0.3	80	0.4
73-88	50	0.4	80	0.5
89-106	50	0.5	100	0.5

> 106**	80	0.4	120	0.5
* Must use vial. Minimum delivery for pen is 0.3 ml. ** For patients > 120 kg, use 80 µg/0.5 ml vial				

Duration of treatment
For patients who exhibit virological response at Week 12, treatment should be continued for at least another three-month period (i.e., a total of six months). The decision to extend therapy to one year of treatment should be based on prognostic factors (e.g., genotype, age > 40 years, male gender, bridging fibrosis).

Dose modification for all patients
If severe adverse reactions or laboratory abnormalities develop during treatment with PegIntron monotherapy or PegIntron in combination with ribavirin, modify the dosages of each product as appropriate, until the adverse reactions abate. Guidelines were developed in clinical trials for dose modification.

Combination Therapy Dose Reduction Guidelines

Table 2a Dose modification guidelines for combination therapy (with ribavirin)

Laboratory values	**Reduce only ribavirin dose to 600 mg/day* if:**	**Reduce only PegIntron dose to one-half dose if:**	**Discontinue combination therapy if:**
Haemoglobin	< 10 g/dl	-	< 8.5 g/dl
Haemoglobin in: Patients with history of stable cardiac disease	≥ 2 g/dl decrease in haemoglobin during any four week period during treatment (permanent dose reduction)		< 12 g/dl after four weeks of dose reduction
White blood cells	-	< 1.5 x 10^9/l	< 1.0 x 10^9/l
Neutrophils	-	< 0.75 x 10^9/l	< 0.5 x 10^9/l
Platelets	-	< 50 x 10^9/l	< 25 x 10^9/l
Bilirubin – direct	-	-	2.5 x ULN**
Bilirubin – indirect	> 5 mg/dl	-	> 4 mg/dl (for > 4 weeks)
Creatinine	-	-	> 2.0 mg/dl
ALT/AST	-	-	2 x baseline and > 10 x ULN**

* Patients whose dose of ribavirin is reduced to 600 mg daily receive one 200 mg capsule in the morning and two 200 mg capsules in the evening.

** Upper limit of normal

Dose reduction of PegIntron may be accomplished by either reducing the prescribed volume by one-half or by utilizing a lower dose strength as shown in **Table 2b**.

Table 2b – Reduced PegIntron Dosing for Combination Therapy

Body Weight (kg)	**Target Reduced Dose (µg)**	**Vial/Pen Strength (µg/0.5 ml)**	**Administer Once Weekly (ml)**	**Amount Delivered (µg)**
< 40	25	50*	0.25	25
40-50	32	50	0.3	30
51-64	40	50	0.4	40
65-75	50	50	0.5	50
76-85	60	80	0.4	64

> 85	75	100	0.4	80
*Must use vial. Minimum delivery for pen is 0.3 ml.				

PegIntron Monotherapy Dose Reduction Guidelines

Dose modification guidelines for patients who use PegIntron monotherapy are shown in **Table 3a.**

Table 3a Dose modification guidelines for PegIntron monotherapy		
Laboratory values	**Reduce PegIntron to one-half dose if:**	**Discontinue PegIntron if:**
Neutrophils	< 0.75 x 10^9/l	< 0.5 x 10^9/l
Platelets	< 50 x 10^9/l	< 25 x 10^9/l

Dose reduction for patients who use 0.5 μg/kg PegIntron monotherapy must be accomplished by reducing the prescribed volume by one-half. The 50 μg/0.5 ml vial must be used if necessary since the pen can only deliver a minimum volume of 0.3 ml.

For patients who use 1.0 μg/kg PegIntron monotherapy, dose reduction may be accomplished by reducing the prescribed volume by one-half or by utilizing a lower dose strength as shown in **Table 3b**.

Table 3b – Reduced PegIntron Dose for the 1.0 μg/kg Monotherapy Regimen				
Body Weight (kg)	**Target Reduced Dose (μg)**	**Vial/Pen Strength (μg/0.5ml)**	**Administer Once Weekly (ml)**	**Amount Delivered (μg)**
30-35	15	50*	0.15	15
36-45	20	50*	0.20	20
46-56	25	50*	0.25	25
57-72	32	50	0.3	30
73-89	40	50	0.4	40
90-106	50	50	0.5	50
> 106	60	80	0.4	64
*Must use vial. Minimum delivery for pen is 0.3 ml.				

Special populations

Use in renal impairment: The clearance of PegIntron is reduced in patients with significant renal impairment. Patients with creatinine clearance ≤ 50 ml/minute must not be treated with PegIntron (see section **5.2**). It is recommended that patients with moderate renal impairment be closely monitored and that their weekly dose of PegIntron be reduced if medically appropriate.

Use in hepatic impairment: The safety and efficacy of PegIntron therapy has not been evaluated in patients with severe hepatic dysfunction, therefore PegIntron must not be used for these patients.

Use in the elderly (≥ 65 years of age): There are no apparent age-related effects on the pharmacokinetics of PegIntron. Data from elderly patients treated with a single dose of PegIntron suggest no alteration in PegIntron dose is necessary based on age (see section **5.2**).

Use in patients under the age of 18 years: PegIntron is not recommended for use in children or adolescents under the age of 18, as there is no experience in this group.

4.3 Contraindications

- Hypersensitivity to the active substance or to any interferon or to any of the excipients;
- Pregnant women;
- Women who are breast-feeding;
- A history of severe pre-existing cardiac disease, including unstable or uncontrolled cardiac disease in the previous six months (see section **4.4**);
- Severe, debilitating medical conditions, including patients with chronic renal failure or creatinine clearance < 50 ml/minute;
- Autoimmune hepatitis or a history of autoimmune disease;
- Severe hepatic dysfunction or decompensated cirrhosis of the liver;
- Pre-existing thyroid disease unless it can be controlled with conventional treatment;
- Epilepsy and/or compromised central nervous system (CNS) function.

4.4 Special warnings and special precautions for use

There is no experience with PegIntron in combination with ribavirin in patients who have relapsed after interferon alpha + ribavirin therapy.

All patients in the chronic hepatitis C studies had a liver biopsy before inclusion, but in certain cases (i.e. patients with genotype 2 and 3), treatment may be possible without histological confirmation. Current treatment guidelines should be consulted as to whether a liver biopsy is needed prior to commencing treatment.

Acute hypersensitivity: Acute hypersensitivity reactions (e.g., urticaria, angioedema, bronchoconstriction, anaphylaxis) have been observed rarely during interferon alfa-2b therapy. If such a reaction develops during treatment with PegIntron, discontinue treatment and institute appropriate medical therapy immediately. Transient rashes do not necessitate interruption of treatment.

Cardiovascular system: As with interferon alfa-2b, patients with a history of congestive heart failure, myocardial infarction and/or previous or current arrhythmic disorders, receiving PegIntron therapy require close monitoring. It is recommended that patients who have pre-existing cardiac abnormalities have electrocardiograms taken prior to and during the course of treatment. Cardiac arrhythmias (primarily supraventricular) usually respond to conventional therapy but may require discontinuation of PegIntron therapy.

Psychiatric and Central Nervous System (CNS): If treatment with peginterferon alfa-2b is judged necessary in patients with existence or history of severe psychiatric conditions, this should only be initiated after having ensured appropriate individualised diagnostic and therapeutic management of the psychiatric condition.
Severe CNS effects, particularly depression, suicidal ideation and attempted suicide have been observed in some patients during PegIntron therapy. Other CNS effects including aggressive behaviour, confusion and alterations of mental status have been observed with alpha interferon. If patients develop psychiatric or CNS problems, including clinical depression, it is recommended that the patient be carefully monitored due to the potential seriousness of these undesirable effects. If symptoms persist or worsen, discontinue PegIntron therapy.
More significant obtundation and coma, including cases of encephalopathy, have been observed in some patients, usually elderly, treated at higher doses for oncology indications. While these effects are generally reversible, in a few patients full resolution took up to three weeks. Very rarely, seizures have occurred with high doses of interferon alpha.

Liver function: As with all interferons, discontinue treatment with PegIntron in patients who develop prolongation of coagulation markers which might indicate liver decompensation.

Fever: While fever may be associated with the flu-like syndrome reported commonly during interferon therapy, other causes of persistent fever must be ruled out.

Hydration: Adequate hydration must be maintained in patients undergoing PegIntron therapy since hypotension related to fluid depletion has been seen in some patients treated with alpha interferons. Fluid replacement may be necessary.

Pulmonary changes: Pulmonary infiltrates, pneumonitis, and pneumonia, occasionally resulting in fatality, have been observed rarely in interferon alpha treated patients. Any patient developing fever, cough, dyspnea or other respiratory symptoms must have a chest X-ray taken. If the chest X-ray shows pulmonary infiltrates or there is evidence of pulmonary function impairment, the patient is to be monitored closely, and, if appropriate, discontinue interferon alpha. Prompt discontinuation of interferon alpha administration and treatment with corticosteroids appear to be associated with resolution of pulmonary adverse events.

Autoimmune disease: The development of auto-antibodies and autoimmune disorders has been reported during treatment with alpha interferons. Patients predisposed to the development of autoimmune disorders may be at increased risk. Patients with signs or symptoms compatible with autoimmune disorders should be evaluated carefully, and the benefit-risk of continued interferon therapy should be reassessed (see also section **4.4 Thyroid changes** and **4.8**).

Ocular changes: Ophthalmologic disorders, including retinal haemorrhages, cotton wool spots, and retinal artery or vein obstruction have been reported in rare instances after treatment with alpha interferons (see section **4.8**). All patients should have a baseline eye examination. Any patient complaining of ocular symptoms, including loss of visual acuity or visual field must have a prompt and complete eye examination. Periodic visual examinations are recommended during PegIntron therapy, particularly in patients with disorders that may be associated with retinopathy, such as diabetes mellitus or hypertension. Discontinuation of PegIntron should be considered in patients who develop new or worsening ophthalmological disorders.

Thyroid changes: Infrequently, patients treated for chronic hepatitis C with interferon alpha have developed thyroid abnormalities, either hypothyroidism or hyperthyroidism. Determine thyroid stimulating hormone (TSH) levels if, during the course of therapy, a patient develops symptoms consistent with possible thyroid dysfunction. In the presence of thyroid dysfunction, PegIntron treatment may be continued if TSH levels can be maintained in the normal range by medication.

Metabolic disturbances: Hypertriglyceridemia and aggravation of hypertriglyceridemia, sometimes severe, have been observed. Monitoring of lipid levels is, therefore, recommended.

HCV/HIV Coinfection
Patients co-infected with HIV and receiving Highly Active Anti-Retroviral Therapy (HAART) may be at increased risk of developing lactic acidosis. Caution should be used when adding PegIntron and ribavirin to HAART therapy (see ribavirin SPC).
Co-infected patients with advanced cirrhosis receiving HAART may be at increased risk of hepatic decompensation and death. Adding treatment with alfa interferons alone or in combination with ribavirin may increase the risk in this patient subset.

Organ transplant recipients: The safety and efficacy of PegIntron alone or in combination with ribavirin for the treatment of hepatitis C in liver or other organ transplant recipients have not been studied. Preliminary data indicates that interferon alpha therapy may be associated with an increased rate of kidney graft rejection. Liver graft rejection has also been reported.

Other: Due to reports of interferon alpha exacerbating pre-existing psoriatic disease and sarcoidosis, use of PegIntron in patients with psoriasis or sarcoidosis is recommended only if the potential benefit justifies the potential risk.

Laboratory tests: Standard haematologic tests, blood chemistry and a test of thyroid function must be conducted in all patients prior to initiating therapy. Acceptable baseline values that may be considered as a guideline prior to initiation of PegIntron therapy are:

- Platelets ≥ 100,000/mm^3
- Neutrophil count ≥ 1,500/mm^3
- TSH level must be within normal limits

Laboratory evaluations are to be conducted at weeks 2 and 4 of therapy, and periodically thereafter as clinically appropriate.

4.5 Interaction with other medicinal products and other forms of interaction

Results of a single-dose study with PegIntron demonstrated no effect on the activity of cytochrome (CY) P1A2, CYP2C8/9, CYP2D6, and hepatic CYP3A4 or N-acetyl transferase. Caution should be advised in the interpretation of these results as the use of other forms of interferon alpha result in a 50 % reduction in the clearance and thus a doubling of plasma concentrations of theophylline, a substrate of CYP1A2.

No pharmacokinetic interactions were noted between PegIntron and ribavirin in a multiple-dose pharmacokinetic study.

4.6 Pregnancy and lactation

There are no adequate data on the use of interferon alfa-2b in pregnant women. Interferon alfa-2b has been shown to be abortifacient in primates. PegIntron is likely to also cause this effect. PegIntron should not be used during pregnancy (see section **5.3**).

PegIntron is recommended for use in fertile women only when they are using effective contraception during the treatment period.

Lactation: It is not known whether the components of this medicinal product are excreted in human milk. Because of the potential for adverse reactions in nursing infants, nursing must be discontinued prior to initiation of treatment.

Ribavirin is teratogenic and embryocidal and must not be used in pregnant women (see ribavirin SPC, **5.3**).

4.7 Effects on ability to drive and use machines

Patients who develop fatigue, somnolence or confusion during treatment with PegIntron are cautioned to avoid driving or operating machinery.

4.8 Undesirable effects

The safety of PegIntron is evaluated from data from two clinical trials: one with PegIntron monotherapy, one with PegIntron in combination with ribavirin. In both cases, patients were treated for one year.

Table 4 describes the regimens and patient exposure for one year of treatment in patients with no previous exposure to interferon (interferon-naïve patients). Because of a significant overlap in the pattern of undesirable effects with PegIntron monotherapy, groups of patients have been brought together in **Table 5** to show the pattern of reported effects for all monotherapy groups.

Table 4	Regimens and patient exposure	
Treatment	**Regimen**	**Number of patients treated for one year**

PegIntron + ribavirin	PegIntron (1.5 micrograms/kg/week) + ribavirin (> 10.6 mg/kg/day)	188
Interferon alfa-2b + ribavirin	Interferon alfa-2b (3 MIU three times a week) + ribavirin (1,000/1,200 mg/day)	505
PegIntron monotherapy	PegIntron (0.5 microgram/kg/week)	315
	PegIntron (1.0 microgram/kg/week)	297
	PegIntron (1.5 micrograms/kg/week)	304

Table 5 Undesirable effects reported in clinical trials (≥ 10 % of patients in PegIntron + ribavirin group)			
	PegIntron + ribavirin	**Interferon alfa-2b + ribavirin**	**PegIntron monotherapy**
Application site disorder			
Injection site inflammation	20 %	17 %	39-44 %
Injection site reaction	54 %	36 %	7-9 %
Body as a whole			
Headache	58 %	57 %	57-63 %
Fatigue	56 %	59 %	43 %
Rigors	42 %	40 %	33-43 %
Fever	39 %	32 %	29-43 %
Flu-like symptoms	21 %	23 %	18-25 %
Asthenia	28 %	17 %	12-14 %
Weight decrease	30 %	19 %	8-18 %
Gastrointestinal			
Nausea	43 %	31 %	20-23 %
Anorexia	35 %	26 %	10-25 %
Diarrhoea	20 %	13 %	14-17 %
Abdominal pain	12 %	9 %	11 %
Vomiting	16 %	10 %	4-7 %
Musculoskeletal			
Myalgia	49 %	49 %	46-60 %
Arthralgia	31 %	26 %	23-28 %
Musculoskeletal pain	15 %	11 %	11-13 %
Psychiatric			
Depression	34 %	32 %	26 %
Irritability	32 %	34 %	19 %
Insomnia	37 %	41 %	16-19 %
Anxiety	14 %	14 %	8 %
Concentration impaired	18 %	21 %	9-10 %
Emotional lability	11 %	10 %	5 %
Respiratory system			
Pharyngitis	10 %	7 %	3 %
Coughing	14 %	11 %	4 %
Dyspnea	26 %	22 %	5 %
Skin and appendages			
Alopecia	45 %	32 %	20-34 %
Pruritus	27 %	27 %	7-9 %
Skin dry	23 %	21 %	6-9 %
Rash	21 %	21 %	5-7 %
Other			
Dizziness	17 %	16 %	7-12 %
Infection viral	10 %	5 %	4-5 %
Mouth dry	10 %	8 %	4-8 %

Table 6. Undesirable effects reported in clinical trials (1%-< 10% of patients treated with PegIntron + ribavirin or PegIntron monotherapy)		
Body system	**5-10%**	**1-<5%**
Body as a whole	chest pain, RUQ pain, malaise	erythema, injection site pain, flushing, thirst, herpes simplex, face or peripheral oedema, dehydration
Cardiovascular		tachycardia, palpitation, hypotension, hypertension, syncope
Central/peripheral nervous system	paresthesia	hypoaesthesia, hyperaesthesia, hypertonia, decreased libido, confusion, tremor, vertigo, migraine, tinnitus, hearing impairment/loss, ataxia, neuralgia
Endocrine	hypothyroidism,	hyperthyroidism, amenorrhoea, prostatitis, hyperuricemia, hypocalcemia
Gastrointestinal	dyspepsia,	constipation, taste perversion, loose stools, stomatitis, ulcerative stomatitis, gingival bleeding, glossitis, flatulence, hemorrhoids, gastroesophageal reflux, hepatomegaly, bilirubinemia, gingivitis
Haematologic	anaemia, leukopaenia	thrombocytopenia, lymphadenopathy,
Musculoskeletal		arthritis
Ocular		blurred vision, conjunctivitis, lacrimal gland disorder, eye pain
Psychiatric	agitation, nervousness	aggressive behaviour, somnolence, behavior disorder, apathy, appetite increased, sleep disorder, dreaming abnormal
Reproductive	menstrual disorder, menorrhagia	ovarian disorder, vaginal disorder, sexual dysfunction (not specified), impotence, breast pain
Respiratory		nonproductive cough, rhinitis, sinusitis, bronchitis, respiratory disorder, nasal congestion, rhinorrhea, dysphonia, epistaxis
Resistance mechanism		otitis media, fungal infection, bacterial infection
Skin and appendages	increased sweating	erythematous rash, eczema, photosensitivity reaction, maculopapular rash, abnormal hair texture, acne, dermatitis, furunculosis, nail disorder, psoriasis, urticaria
Urinary		micturition frequency, urine abnormal

Most cases of neutropaenia and thrombocytopaenia were mild (WHO grades 1 or 2). There were some cases of more severe neutropaenia in patients treated with the recommended doses of PegIntron in combination with ribavirin (WHO grade 3: 39 of 186 [21 %]; and WHO grade 4: 13 of 186 [7 %]).

In a clinical trial, approximately 1.2 % of patients treated with PegIntron or interferon alfa-2b in combination with ribavirin reported life-threatening psychiatric events during treatment. These events included suicidal ideation and attempted suicide (see section **4.4**). Following marketing, psychosis and hallucinations have been reported rarely.

Rarely reported events with interferon alfa-2b, including PegIntron, include seizure, pancreatitis, arrhythmia, peripheral neuropathy, diabetes, rhabdomyolysis, myositis, renal insufficiency and renal failure.

Cardiovascular (CVS) adverse events, particularly arrhythmia, appeared to be correlated mostly with pre-existing CVS disease and prior therapy with cardiotoxic agents (see section **4.4**). Cardiomyopathy, that may be reversible upon discontinuation of interferon alpha, has been reported rarely in patients without prior evidence of cardiac disease.

Very rarely cases of erythema multiforme, Stevens Johnson syndrome, toxic epidermal necrolysis, cardiac ischaemia, myocardial infarction, cerebrovascular ischaemia, cerebrovascular hemorrhage, encephalopathy, sarcoidosis or exacerbation of sarcoidosis, interstitial lung disease and injection site necrosis have been reported. Ulcerative and ischaemic colitis have been reported very rarely with PegIntron.

Very rarely, interferon alfa-2b or PegIntron used alone or in combination with ribavirin may be associated with aplastic anaemia.

Ophthalmological disorders that have been reported rarely with alpha interferons include retinopathies (including macular oedema), retinal haemorrhages, retinal artery or vein obstruction, cotton wool spots, loss of visual acuity or visual field, optic neuritis, and papilloedema (see section **4.4**).

A wide variety of autoimmune and immune-mediated disorders have been reported with alpha interferons including thyroid disorders, idiopathic and thrombotic thrombocytopenic purpura, vasculitis, neuropathies including mononeuropathies (see also section **4.4**, **Autoimmune disorders**).

4.9 Overdose

In clinical trials, cases of accidental overdose, at never more than twice the prescribed dose, were reported. There were no serious reactions. Undesirable effects resolved during continued administration of PegIntron.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunostimulants, Cytokines and immunomodulators, Interferons, Peginterferon alfa-2b, ATC code: L03A B10.

Recombinant interferon alfa-2b is covalently conjugated with monomethoxy polyethylene glycol at an average degree of substitution of 1 mole of polymer/mole of protein. The average molecular mass is approximately 31,300 daltons of which the protein moiety constitutes approximately 19,300.

Interferon alfa-2b
In vitro and *in vivo* studies suggest that the biological activity of PegIntron is derived from its interferon alfa-2b moiety.

Interferons exert their cellular activities by binding to specific membrane receptors on the cell surface. Studies with other interferons have demonstrated species specificity. However, certain monkey species, e.g., Rhesus monkeys, are susceptible to pharmacodynamic stimulation upon exposure to human type 1 interferons.

Once bound to the cell membrane, interferon initiates a complex sequence of intracellular events that include the induction of certain enzymes. It is thought that this process, at least in part, is responsible for the various cellular responses to interferon, including inhibition of virus replication in virus-infected cells, suppression of cell proliferation and such immunomodulating activities as enhancement

of the phagocytic activity of macrophages and augmentation of the specific cytotoxicity of lymphocytes for target cells. Any or all of these activities may contribute to interferon's therapeutic effects.

Recombinant interferon alfa-2b also inhibits viral replication *in vitro* and *in vivo*. Although the exact antiviral mode of action of recombinant interferon alfa-2b is unknown, it appears to alter the host cell metabolism. This action inhibits viral replication or if replication occurs, the progeny virions are unable to leave the cell.

PegIntron
PegIntron pharmacodynamics were assessed in a rising single-dose trial in healthy subjects by examining changes in oral temperature, concentrations of effector proteins such as serum neopterin and 2'5'-oligoadenylate synthetase (2'5'-OAS), as well as white cell and neutrophil counts. Subjects treated with PegIntron showed mild dose-related elevations in body temperature. Following single doses of PegIntron between 0.25 and 2.0 micrograms/kg/week, serum neopterin concentration was increased in a dose-related manner. Neutrophil and white cell count reductions at the end of week 4 correlated with the dose of PegIntron.

PegIntron clinical trials
Two pivotal trials have been conducted, one (C/I97-010) with PegIntron monotherapy; the other (C/I98-580) with PegIntron in combination with ribavirin. Eligible patients for these trials had chronic hepatitis C confirmed by a positive HCV-RNA polymerase chain reaction (PCR) assay (> 30 IU/ml), a liver biopsy consistent with a histological diagnosis of chronic hepatitis with no other cause for the chronic hepatitis, and abnormal serum ALT.

In the PegIntron monotherapy trial, a total of 916 naïve chronic hepatitis C patients were treated with PegIntron (0.5, 1.0 or 1.5 micrograms/kg/week) for one year with a follow-up period of six months. In addition, 303 patients received interferon alfa-2b (3 million International Units [MIU] three times a week as a comparator. This study showed that PegIntron was superior to interferon alfa-2b (**Table 7**).

In the PegIntron combination trial, 1,530 naïve patients were treated for one year with one of the following combination regimens:
- PegIntron (1.5 micrograms/kg/week) + ribavirin (800 mg/day), (n = 511).
- PegIntron (1.5 micrograms/kg/week for one month followed by 0.5 microgram/kg/week for 11 months) + ribavirin (1,000/1,200 mg/day), (n = 514).
- Interferon alfa-2b (3 MIU three times a week) + ribavirin (1,000/1,200 mg/day) (n = 505).

In this trial, the combination of PegIntron (1.5 micrograms/kg/week) and ribavirin was significantly more effective than the combination of interferon alfa-2b and ribavirin (**Table 7**), particularly in patients infected with Genotype 1 (**Table 8**). Sustained response was assessed by the response rate six months after the cessation of treatment.

HCV genotype and baseline virus load are prognostic factors which are known to affect response rates. However, response rates in this trial were shown to be dependent also on the dose of ribavirin administered in combination with PegIntron or interferon alfa-2b. In those patients that received > 10.6 mg/kg ribavirin (800 mg dose in typical 75 kg patient), regardless of genotype or viral load, response rates were significantly higher than in those patients that received ≤ 10.6 mg/kg ribavirin (**Table 8**), while response rates in patients that received > 13.2 mg/kg ribavirin were even higher.

Table 7 Sustained virological response (% patients HCV negative)

	PegIntron monotherapy				**PegIntron + ribavirin**		
Treatment regimen	**P 1.5**	**P 1.0**	**P 0.5**	**I**	**P 1.5/R**	**P 0.5/R**	**I/R**
Number of patients	304	297	315	303	511	514	505
Response at end of treatment	49 %	41 %	33 %	24 %	65 %	56 %	54 %

Sustained response	**23 %***	**25 %**	**18 %**	**12 %**	**54 %****	**47 %**	**47 %**

P 1.5 PegIntron 1.5 micrograms/kg
P 1.0 PegIntron 1.0 microgram/kg
P 0.5 PegIntron 0.5 microgram/kg
I Interferon alfa-2b 3 MIU
P 1.5/R PegIntron (1.5 micrograms/kg) + ribavirin (800 mg)
P 0.5/R PegIntron (1.5 to 0.5 microgram/kg) + ribavirin (1,000/1,200 mg)
I/R Interferon alfa-2b (3 MIU) + ribavirin (1,000/1,200 mg)
* $p < 0.001$ P 1.5 vs. I
** $p = 0.0143$ P 1.5/R vs. I/R

Table 8 Sustained response rates with PegIntron + ribavirin (by ribavirin dose, genotype and viral load)

HCV Genotype	Rebetol dose (mg/kg)	P 1.5/R	P 0.5/R	I/R
All Genotypes	**All**	**54 %**	**47 %**	**47 %**
	≤ 10.6	50 %	41 %	27 %
	> 10.6	61 %	48 %	47 %
Genotype 1	**All**	**42 %**	**34 %**	**33 %**
	≤ 10.6	38 %	25 %	20 %
	> 10.6	48 %	34 %	34 %
Genotype 1 ≤ 600,000 IU/ml	All	73 %	51 %	45 %
	≤ 10.6	74 %	25 %	33 %
	> 10.6	71 %	52 %	45 %
Genotype 1 > 600,000 IU/ml	All	30 %	27 %	29 %
	≤ 10.6	27 %	25 %	17 %
	> 10.6	37 %	27 %	29 %
Genotype 2/3	**All**	**82 %**	**80 %**	**79 %**
	≤ 10.6	79 %	73 %	50 %
	> 10.6	88 %	80 %	80 %

P 1.5/R PegIntron (1.5 micrograms/kg) + ribavirin (800 mg)
P 0.5/R PegIntron (1.5 to 0.5 microgram/kg) + ribavirin (1,000/1,200 mg)
I/R Interferon alfa-2b (3 MIU) + ribavirin (1,000/1,200 mg)

In the PegIntron monotherapy study, the Quality of Life was generally less affected by 0.5 microgram/kg of PegIntron than by either 1.0 microgram/kg of PegIntron once weekly or 3 MIU of interferon alfa-2b three times a week.

In a separate trial, 224 patients with genotype 2 or 3 received PegIntron, 1.5 microgram/kg subcutaneously, once weekly, in combination with ribavirin 800 mg –1,400 mg p.o. for 6 months (based on body weight, only three patients weighing > 105 kg, received the 1,400 mg dose, which has not yet been validated) (**Table 9**). Twenty-four % had bridging fibrosis or cirrhosis (Knodell 3/4).

Table 9. Virologic Response at End of Treatment, Sustained Virologic Response and Relapse by HCV Genotype and Viral Load*

	PegIntron 1.5 µg/kg Once Weekly Plus Rebetol 800-1400 mg/day		
	End of Treatment Response	Sustained Virologic Response	Relapse
All Subjects	94 % (211/224)	81 % (182/224)	12 % (27/224)
HCV 2	100 % (42/42)	93 % (39/42)	7 % (3/42)
≤ 600,000 IU/ml	100 % (20/20)	95 % (19/20)	5 % (1/20)
> 600,000 IU/mL	100 % (22/22)	91 % (20/22)	9 % (2/22)
HCV 3	93 % (169/182)	79 % (143/182)	14 %

			(24/166)
≤ 600,000 IU/ml	93 % (92/99)	86 % (85/99)	8 % (7/91)
> 600,000 IU/ml	93 % (77/83)	70 % (58/83)	23 % (17/75)

* Any subject with an undetectable HCV-RNA level at the Follow-Up Week 12 visit and missing data at the Follow-Up Week 24 visit was considered a sustained responder. Any subject with missing data in and after the Follow-Up Week 12 window was considered to be a non-responder at Week 24 of follow-up.

The 6 month treatment duration in this trial was better tolerated than one year of treatment in the pivotal combination trial; for discontinuation 5 % vs. 14 %, for dose modification 18 % vs. 49 %.

Predictability of sustained virological response
Virological reponse by week 12, defined as a 2-log viral load decrease or undetectable levels of HCV RNA has been shown to be predictive for sustained response (**Table 10**).

Table 10 Predictability of sustained response by viral response at week 12 and genotype*

Treatment	Genotype	Viral response at week 12	Sustained response	Negative predictive value
PegIntron 1.5 + ribavirin (> 10.6 mg/kg) 48-week treatment	1	Yes 75 % (82/110)	71 % (58/82)	----
		No 25 % (28/110)	0 % (0/28)	100 %
PegIntron 1.5 + ribavirin 800-1,400 mg 24-week treatment	2 and 3	Yes 99 % (213/215)	83 % (177/213)	----
		No 1 % (2/215)	50 % (1/2)	50 %

* reflects patients with 12 week data available

The negative predictive value for sustained response in patients treated with PegIntron in monotherapy was 98 %.

5.2 Pharmacokinetic properties

PegIntron is a well characterized polyethylene glycol-modified ("pegylated") derivative of interferon alfa-2b and is predominantly composed of monopegylated species. The plasma half-life of PegIntron is prolonged compared with non-pegylated interferon alfa-2b. PegIntron has a potential to depegylate to free interferon alfa-2b. The biologic activity of the pegylated isomers is qualitatively similar, but weaker than free interferon alfa-2b.

Following subcutaneous administration, maximal serum concentrations occur between 15-44 hours post-dose, and are sustained for up to 48-72 hours post-dose.

PegIntron C_{max} and AUC measurements increase in a dose-related manner. Mean apparent volume of distribution is 0.99 l/kg.

Upon multiple dosing, there is an accumulation of immunoreactive interferons. There is, however, only a modest increase in biologic activity as measured by a bioassay.

Mean (SD) PegIntron elimination half-life is approximately 40 hours (13.3 hours), with apparent clearance of 22.0 ml/hr·kg. The mechanisms involved in clearance of interferons in man have not yet been fully elucidated. However, renal elimination may account for a minority (approximately 30 %) of PegIntron apparent clearance.

Renal function: Renal clearance appears to account for 30 % of total clearance of PegIntron. In a single dose study (1.0 microgram/kg) in patients with impaired renal function, C_{max}, AUC, and half-life increased in relation to the degree of renal impairment.

Based on these data, no dose modification is recommended based on creatinine clearance. However, because of marked intra-subject variability in interferon pharmacokinetics, it is recommended that patients be monitored closely during treatment with PegIntron (see section **4.2**). Patients with severe renal dysfunction or creatinine clearance < 50 ml/min must not be treated with PegIntron.

Hepatic function: The pharmacokinetics of PegIntron have not been evaluated in patients with severe hepatic dysfunction.

Elderly patients ≥ 65 years of age: The pharmacokinetics of PegIntron following a single subcutaneous dose of 1.0 microgram/kg were not affected by age. The data suggest that no alteration in PegIntron dosage is necessary based on advancing age.

Patients under the age of 18 years: Specific pharmacokinetic evaluations have not been performed on these patients. PegIntron is indicated for the treatment of chronic hepatitis C only in patients 18 years of age or older.

Interferon neutralising factors: Interferon neutralising factor assays were performed on serum samples of patients who received PegIntron in the clinical trial. Interferon neutralising factors are antibodies which neutralise the antiviral activity of interferon. The clinical incidence of neutralising factors in patients who received PegIntron 0.5 micrograms/kg is 1.1 %.

5.3 Preclinical safety data

PegIntron: Adverse events not observed in clinical trials were not seen in toxicity studies in monkeys. These studies were limited to four weeks due to the appearance of anti-interferon antibodies in most monkeys.

Reproduction studies of PegIntron have not been performed. Interferon alfa-2b has been shown to be an abortifacient in primates. PegIntron is likely to also cause this effect. Effects on fertility have not been determined. PegIntron showed no genotoxic potential. (see section **4.6** for relevant human data. It is not known whether the components of this medicinal product are excreted in human milk. Therefore, nursing must be discontinued prior to the initiation of therapy.)

The relative non-toxicity of monomethoxy-polyethylene glycol (mPEG), which is liberated from PegIntron by metabolism *in vivo* has been demonstrated in preclinical acute and subchronic toxicity studies in rodents and monkeys, standard embryo-foetal development studies and in *in vitro* mutagenicity assays.

PegIntron plus ribavirin: When used in combination with ribavirin, PegIntron did not cause any effects not previously seen with either active substance alone. The major treatment-related change was a reversible, mild to moderate anaemia, the severity of which was greater than that produced by either active substance alone.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder for solution for injection:

Disodium phosphate, anhydrous,
Sodium dihydrogen phosphate dihydrate,
Sucrose,

Polysorbate 80.
Solvent for parenteral use:
Water for injections.

Deliverable volume from pen = 0.5 ml. An overfill is also included for proper dispensing from the pen delivery system.

6.2 Incompatibilities

This medicinal product should only be reconstituted with the solvent provided and must not be mixed with other medicinal products (see also section **6.6**).

6.3 Shelf life

3 years

After reconstitution:
- Chemical and physical in-use stability has been demonstrated for 24 hours at 2°C - 8ºC.
- From a microbiological point of view, the product is to be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C - 8°C.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C). Do not freeze.

6.5 Nature and contents of container

The powder and solvent are both contained in a two-chamber cartridge, Type I flint glass, separated by a bromobutyl rubber plunger. The cartridge is sealed at one end with a polypropylene cap containing a bromobutyl rubber liner and at the other end by a bromobutyl rubber plunger.

PegIntron 50 micrograms is supplied as:
- 1 pen containing powder and solvent for solution for injection, 1 injection needle and 2 cleansing swabs;
- 4 pens containing powder and solvent for solution for injection, 4 injection needles and 8 cleansing swabs;
- 6 pens containing powder and solvent for solution for injection, 6 injection needles and 12 cleansing swabs;
- 12 pens containing powder and solvent for solution for injection, 12 injection needles and 24 cleansing swabs.

Not all pack sizes may be marketed.

6.6 Instructions for use and handling and disposal

PegIntron pre-filled pen contains a powder of peginterferon alfa-2b and a solvent for solution at a strength of 50 micrograms for single use. Each pen is reconstituted with the solvent provided in the two-chamber cartridge (water for injections) for administration of up to 0.5 ml of solution. A small volume is lost during preparation of PegIntron for injection when the dose is measured and injected. Therefore, each pen contains an excess amount of solvent and PegIntron powder to ensure delivery of the labelled dose in 0.5 ml of PegIntron, solution for injection. The reconstituted solution has a concentration of 50 micrograms in 0.5 ml.

PegIntron is injected subcutaneously after reconstituting the powder as instructed, attaching an injection needle and setting the prescribed dose. A complete and illustrated set of instructions is provided in the Annex to the Package Leaflet.

Remove PegIntron pre-filled pen from the refrigerator before administration to allow the solvent to reach room temperature (not more than 25°C).

As for all parenteral medicinal products, inspect visually the reconstituted solution prior to administration. The reconstituted solution should be clear and colourless. Do not use if discolouration or particulate matter is present. After administering the dose, discard the PegIntron pre- filled pen and any unused solution contained in it.

7. MARKETING AUTHORISATION HOLDER

SP Europe
73, rue de Stalle
B-1180 Bruxelles
Belgium

8. MARKETING AUTHORISATION NUMBERS

EU/1/00/131/031
EU/1/00/131/032
EU/1/00/131/033
EU/1/00/131/034

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

6 February 2002

10. DATE OF REVISION OF THE TEXT

1. NAME OF THE MEDICINAL PRODUCT

PegIntron 80 micrograms, powder and solvent for solution for injection in pre-filled pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled pen of PegIntron 80 micrograms contains a sufficient amount of peginterferon alfa-2b as measured on a protein basis in a powder for solution for injection, and the corresponding amount of solvent, to provide 80 micrograms in 0.5 ml of peginterferon alfa-2b when reconstituted as recommended.

The active substance is a covalent conjugate of recombinant interferon alfa-2b* with monomethoxy polyethylene glycol. The potency of this product should not be compared to that of another pegylated or non-pegylated protein of the same therapeutic class. For more information, see section **5.1.**
*produced by rDNA technology in *E.coli* cells harbouring a genetically engineered plasmid hybrid encompassing an interferon alfa-2b gene from human leukocytes

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection
The white powder and the clear and colourless solvent are both contained in a two-chamber glass cartidge assembled into a single use pre-filled pen.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PegIntron is indicated for the treatment of adult patients with chronic hepatitis C who have elevated transaminases without liver decompensation and who are positive for serum HCV-RNA or anti-HCV (see section **4.4**).

The best way to use PegIntron in this indication is in combination with ribavirin.

This combination is indicated in naïve patients as well as in patients who have previously responded (with normalisation of ALT at the end of treatment) to interferon alpha monotherapy but who have subsequently relapsed.

Interferon monotherapy, including PegIntron, is indicated mainly in case of intolerance or contraindication to ribavirin.

Please refer also to the ribavirin Summary of Product Characteristics (SPC) when PegIntron is to be used in combination with ribavirin.

4.2 Posology and method of administration

Treatment should be initiated and monitored only by a physician experienced in the management of patients with hepatitis C.

Dose to be administered
PegIntron should be administered as a once weekly subcutaneous injection. The dose administered depends on whether it is used in combination with ribavirin or as monotherapy.

Combination therapy

PegIntron 1.5 micrograms/kg/week in combination with ribavirin capsules.

The intended dose of 1.5 μg/kg of PegIntron to be used in combination with ribavirin may be delivered in weight categories with the pen/vial strengths according to **Table 1**. Ribavirin capsules are to be administered orally each day in two divided doses with food (morning and evening).

Table 1 - Dosing for Combination Therapy

Body Weight (kg)	**PegIntron**		**Ribavirin Capsules**	
	Vial/Pen Strength (μg/0.5ml)	**Administer Once Weekly (ml)**	**Total Daily Dose (mg)**	**Number of Capsules (200 mg)**
< 40	50	0.5	800	4[a]
40-50	80	0.4	800	4[a]
51-64	80	0.5	800	4[a]
65-75	100	0.5	1,000	5[b]
76-85	120	0.5	1,000	5[b]
> 85	150	0.5	1,200	6[c]

a: 2 morning, 2 evening
b: 2 morning, 3 evening
c: 3 morning, 3 evening

Duration of treatment
Predictability of sustained virological response: Patients infected with virus genotype 1 who fail to achieve virological response at Week 12 are highly unlikely to become sustained virological responders (see also section **5.1**).

- **Genotype 1**: For patients who exhibit virological response at week 12, treatment should be continued for another nine month period (i.e., a total of 48 weeks).
- **Genotypes 2 or 3**: It is recommended that all patients be treated for 24 weeks.
- **Genotype 4:** In general, patients infected with genotype 4 are considered harder to treat and limited study data (n=66) indicate they are compatible with a posology as for genotype 1.

PegIntron monotherapy
As monotherapy the PegIntron regimen is 0.5 or 1.0 microgram/kg/week. The lowest vial or pen strength available is 50 μg/0.5 ml; therefore for patients prescribed 0.5 μg/kg/week, doses must be adjusted by volume as shown in **Table 2**. For the 1.0 μg/kg dose, similar volume adjustments can be made or alternate vial strengths can be used as shown in **Table 2**.

Table 2- Monotherapy Dosing

	0.5 μg/kg		**1.0 μg/kg**	
Body Weight (kg)	**Vial/Pen Strength (μg/0.5ml)**	**Administer Once Weekly (ml)**	**Vial/Pen Strength (μg/0.5ml)**	**Administer Once Weekly (ml)**
30-35	50*	0.15	50	0.3
36-45	50*	0.2	50	0.4
46-56	50*	0.25	50	0.5
57-72	50	0.3	80	0.4
73-88	50	0.4	80	0.5
89-106	50	0.5	100	0.5

> 106**	80	0.4	120	0.5
* Must use vial. Minimum delivery for pen is 0.3 ml. ** For patients > 120 kg, use 80 µg/0.5 ml vial				

Duration of treatment
For patients who exhibit virological response at Week 12, treatment should be continued for at least another three-month period (i.e., a total of six months). The decision to extend therapy to one year of treatment should be based on prognostic factors (e.g., genotype, age > 40 years, male gender, bridging fibrosis).

Dose modification for all patients
If severe adverse reactions or laboratory abnormalities develop during treatment with PegIntron monotherapy or PegIntron in combination with ribavirin, modify the dosages of each product as appropriate, until the adverse reactions abate. Guidelines were developed in clinical trials for dose modification.

Combination Therapy Dose Reduction Guidelines

Table 2a Dose modification guidelines for combination therapy (with ribavirin)

Laboratory values	**Reduce only ribavirin dose to 600 mg/day* if:**	**Reduce only PegIntron dose to one-half dose if:**	**Discontinue combination therapy if:**
Haemoglobin	< 10 g/dl	-	< 8.5 g/dl
Haemoglobin in: Patients with history of stable cardiac disease	≥ 2 g/dl decrease in haemoglobin during any four week period during treatment (permanent dose reduction)		< 12 g/dl after four weeks of dose reduction
White blood cells	-	< 1.5 x 10^9/l	< 1.0 x 10^9/l
Neutrophils	-	< 0.75 x 10^9/l	< 0.5 x 10^9/l
Platelets	-	< 50 x 10^9/l	< 25 x 10^9/l
Bilirubin – direct	-	-	2.5 x ULN**
Bilirubin – indirect	> 5 mg/dl	-	> 4 mg/dl (for > 4 weeks)
Creatinine	-	-	> 2.0 mg/dl
ALT/AST	-	-	2 x baseline and > 10 x ULN**

* Patients whose dose of ribavirin is reduced to 600 mg daily receive one 200 mg capsule in the morning and two 200 mg capsules in the evening.

** Upper limit of normal

Dose reduction of PegIntron may be accomplished by either reducing the prescribed volume by one-half or by utilizing a lower dose strength as shown in **Table 2b**.

Table 2b – Reduced PegIntron Dosing for Combination Therapy

Body Weight (kg)	**Target Reduced Dose (µg)**	**Vial/Pen Strength (µg/0.5 ml)**	**Administer Once Weekly (ml)**	**Amount Delivered (µg)**
< 40	25	50*	0.25	25
40-50	32	50	0.3	30
51-64	40	50	0.4	40
65-75	50	50	0.5	50
76-85	60	80	0.4	64

> 85	75	100	0.4	80
*Must use vial. Minimum delivery for pen is 0.3 ml.				

PegIntron Monotherapy Dose Reduction Guidelines

Dose modification guidelines for patients who use PegIntron monotherapy are shown in **Table 3a.**

Table 3a Dose modification guidelines for PegIntron monotherapy		
Laboratory values	**Reduce PegIntron to one-half dose if:**	**Discontinue PegIntron if:**
Neutrophils	< 0.75 x 10^9/l	< 0.5 x 10^9/l
Platelets	< 50 x 10^9/l	< 25 x 10^9/l

Dose reduction for patients who use 0.5 µg/kg PegIntron monotherapy must be accomplished by reducing the prescribed volume by one-half. The 50 µg/0.5 ml vial must be used if necessary since the pen can only deliver a minimum volume of 0.3 ml.

For patients who use 1.0 µg/kg PegIntron monotherapy, dose reduction may be accomplished by reducing the prescribed volume by one-half or by utilizing a lower dose strength as shown in **Table 3b**.

Table 3b – Reduced PegIntron Dose for the 1.0 µg/kg Monotherapy Regimen				
Body Weight (kg)	**Target Reduced Dose (µg)**	**Vial/Pen Strength (µg/0.5ml)**	**Administer Once Weekly (ml)**	**Amount Delivered (µg)**
30-35	15	50*	0.15	15
36-45	20	50*	0.20	20
46-56	25	50*	0.25	25
57-72	32	50	0.3	30
73-89	40	50	0.4	40
90-106	50	50	0.5	50
> 106	60	80	0.4	64
*Must use vial. Minimum delivery for pen is 0.3 ml.				

Special populations

Use in renal impairment: The clearance of PegIntron is reduced in patients with significant renal impairment. Patients with creatinine clearance ≤ 50 ml/minute must not be treated with PegIntron (see section **5.2**). It is recommended that patients with moderate renal impairment be closely monitored and that their weekly dose of PegIntron be reduced if medically appropriate.

Use in hepatic impairment: The safety and efficacy of PegIntron therapy has not been evaluated in patients with severe hepatic dysfunction, therefore PegIntron must not be used for these patients.

Use in the elderly (≥ 65 years of age): There are no apparent age-related effects on the pharmacokinetics of PegIntron. Data from elderly patients treated with a single dose of PegIntron suggest no alteration in PegIntron dose is necessary based on age (see section **5.2**).

Use in patients under the age of 18 years: PegIntron is not recommended for use in children or adolescents under the age of 18, as there is no experience in this group.

4.3 Contraindications

- Hypersensitivity to the active substance or to any interferon or to any of the excipients;
- Pregnant women;
- Women who are breast-feeding;
- A history of severe pre-existing cardiac disease, including unstable or uncontrolled cardiac disease in the previous six months (see section **4.4**);
- Severe, debilitating medical conditions, including patients with chronic renal failure or creatinine clearance < 50 ml/minute;
- Autoimmune hepatitis or a history of autoimmune disease;
- Severe hepatic dysfunction or decompensated cirrhosis of the liver;
- Pre-existing thyroid disease unless it can be controlled with conventional treatment;
- Epilepsy and/or compromised central nervous system (CNS) function.

4.4 Special warnings and special precautions for use

There is no experience with PegIntron in combination with ribavirin in patients who have relapsed after interferon alpha + ribavirin therapy.

All patients in the chronic hepatitis C studies had a liver biopsy before inclusion, but in certain cases (i.e. patients with genotype 2 and 3), treatment may be possible without histological confirmation. Current treatment guidelines should be consulted as to whether a liver biopsy is needed prior to commencing treatment.

Acute hypersensitivity: Acute hypersensitivity reactions (e.g., urticaria, angioedema, bronchoconstriction, anaphylaxis) have been observed rarely during interferon alfa-2b therapy. If such a reaction develops during treatment with PegIntron, discontinue treatment and institute appropriate medical therapy immediately. Transient rashes do not necessitate interruption of treatment.

Cardiovascular system: As with interferon alfa-2b, patients with a history of congestive heart failure, myocardial infarction and/or previous or current arrhythmic disorders, receiving PegIntron therapy require close monitoring. It is recommended that patients who have pre-existing cardiac abnormalities have electrocardiograms taken prior to and during the course of treatment. Cardiac arrhythmias (primarily supraventricular) usually respond to conventional therapy but may require discontinuation of PegIntron therapy.

Psychiatric and Central Nervous System (CNS): If treatment with peginterferon alfa-2b is judged necessary in patients with existence or history of severe psychiatric conditions, this should only be initiated after having ensured appropriate individualised diagnostic and therapeutic management of the psychiatric condition.
Severe CNS effects, particularly depression, suicidal ideation and attempted suicide have been observed in some patients during PegIntron therapy. Other CNS effects including aggressive behaviour, confusion and alterations of mental status have been observed with alpha interferon. If patients develop psychiatric or CNS problems, including clinical depression, it is recommended that the patient be carefully monitored due to the potential seriousness of these undesirable effects. If symptoms persist or worsen, discontinue PegIntron therapy.
More significant obtundation and coma, including cases of encephalopathy, have been observed in some patients, usually elderly, treated at higher doses for oncology indications. While these effects are generally reversible, in a few patients full resolution took up to three weeks. Very rarely, seizures have occurred with high doses of interferon alpha.

Liver function: As with all interferons, discontinue treatment with PegIntron in patients who develop prolongation of coagulation markers which might indicate liver decompensation.

Fever: While fever may be associated with the flu-like syndrome reported commonly during interferon therapy, other causes of persistent fever must be ruled out.

Hydration: Adequate hydration must be maintained in patients undergoing PegIntron therapy since hypotension related to fluid depletion has been seen in some patients treated with alpha interferons. Fluid replacement may be necessary.

Pulmonary changes: Pulmonary infiltrates, pneumonitis, and pneumonia, occasionally resulting in fatality, have been observed rarely in interferon alpha treated patients. Any patient developing fever, cough, dyspnea or other respiratory symptoms must have a chest X-ray taken. If the chest X-ray shows pulmonary infiltrates or there is evidence of pulmonary function impairment, the patient is to be monitored closely, and, if appropriate, discontinue interferon alpha. Prompt discontinuation of interferon alpha administration and treatment with corticosteroids appear to be associated with resolution of pulmonary adverse events.

Autoimmune disease: The development of auto-antibodies and autoimmune disorders has been reported during treatment with alpha interferons. Patients predisposed to the development of autoimmune disorders may be at increased risk. Patients with signs or symptoms compatible with autoimmune disorders should be evaluated carefully, and the benefit-risk of continued interferon therapy should be reassessed (see also section **4.4 Thyroid changes** and **4.8**).

Ocular changes: Ophthalmologic disorders, including retinal haemorrhages, cotton wool spots, and retinal artery or vein obstruction have been reported in rare instances after treatment with alpha interferons (see section **4.8**). All patients should have a baseline eye examination. Any patient complaining of ocular symptoms, including loss of visual acuity or visual field must have a prompt and complete eye examination. Periodic visual examinations are recommended during PegIntron therapy, particularly in patients with disorders that may be associated with retinopathy, such as diabetes mellitus or hypertension. Discontinuation of PegIntron should be considered in patients who develop new or worsening ophthalmological disorders.

Thyroid changes: Infrequently, patients treated for chronic hepatitis C with interferon alpha have developed thyroid abnormalities, either hypothyroidism or hyperthyroidism. Determine thyroid stimulating hormone (TSH) levels if, during the course of therapy, a patient develops symptoms consistent with possible thyroid dysfunction. In the presence of thyroid dysfunction, PegIntron treatment may be continued if TSH levels can be maintained in the normal range by medication.

Metabolic disturbances: Hypertriglyceridemia and aggravation of hypertriglyceridemia, sometimes severe, have been observed. Monitoring of lipid levels is, therefore, recommended.

HCV/HIV Coinfection
Patients co-infected with HIV and receiving Highly Active Anti-Retroviral Therapy (HAART) may be at increased risk of developing lactic acidosis. Caution should be used when adding PegIntron and ribavirin to HAART therapy (see ribavirin SPC).
Co-infected patients with advanced cirrhosis receiving HAART may be at increased risk of hepatic decompensation and death. Adding treatment with alfa interferons alone or in combination with ribavirin may increase the risk in this patient subset.

Organ transplant recipients: The safety and efficacy of PegIntron alone or in combination with ribavirin for the treatment of hepatitis C in liver or other organ transplant recipients have not been studied. Preliminary data indicates that interferon alpha therapy may be associated with an increased rate of kidney graft rejection. Liver graft rejection has also been reported.

Other: Due to reports of interferon alpha exacerbating pre-existing psoriatic disease and sarcoidosis, use of PegIntron in patients with psoriasis or sarcoidosis is recommended only if the potential benefit justifies the potential risk.

Laboratory tests: Standard haematologic tests, blood chemistry and a test of thyroid function must be conducted in all patients prior to initiating therapy. Acceptable baseline values that may be considered as a guideline prior to initiation of PegIntron therapy are:

- Platelets ≥ 100,000/mm^3
- Neutrophil count ≥ 1,500/mm^3
- TSH level must be within normal limits

Laboratory evaluations are to be conducted at weeks 2 and 4 of therapy, and periodically thereafter as clinically appropriate.

4.5 Interaction with other medicinal products and other forms of interaction

Results of a single-dose study with PegIntron demonstrated no effect on the activity of cytochrome (CY) P1A2, CYP2C8/9, CYP2D6, and hepatic CYP3A4 or N-acetyl transferase. Caution should be advised in the interpretation of these results as the use of other forms of interferon alpha result in a 50 % reduction in the clearance and thus a doubling of plasma concentrations of theophylline, a substrate of CYP1A2.

No pharmacokinetic interactions were noted between PegIntron and ribavirin in a multiple-dose pharmacokinetic study.

4.6 Pregnancy and lactation

There are no adequate data on the use of interferon alfa-2b in pregnant women. Interferon alfa-2b has been shown to be abortifacient in primates. PegIntron is likely to also cause this effect. PegIntron should not be used during pregnancy (see section **5.3**).

PegIntron is recommended for use in fertile women only when they are using effective contraception during the treatment period.

Lactation: It is not known whether the components of this medicinal product are excreted in human milk. Because of the potential for adverse reactions in nursing infants, nursing must be discontinued prior to initiation of treatment.

Ribavirin is teratogenic and embryocidal and must not be used in pregnant women (see ribavirin SPC, **5.3**).

4.7 Effects on ability to drive and use machines

Patients who develop fatigue, somnolence or confusion during treatment with PegIntron are cautioned to avoid driving or operating machinery.

4.8 Undesirable effects

The safety of PegIntron is evaluated from data from two clinical trials: one with PegIntron monotherapy, one with PegIntron in combination with ribavirin. In both cases, patients were treated for one year.

Table 4 describes the regimens and patient exposure for one year of treatment in patients with no previous exposure to interferon (interferon-naïve patients). Because of a significant overlap in the pattern of undesirable effects with PegIntron monotherapy, groups of patients have been brought together in **Table 5** to show the pattern of reported effects for all monotherapy groups.

Table 4	Regimens and patient exposure	
Treatment	**Regimen**	**Number of patients treated for one year**

PegIntron + ribavirin	PegIntron (1.5 micrograms/kg/week) + ribavirin (> 10.6 mg/kg/day)	188
Interferon alfa-2b + ribavirin	Interferon alfa-2b (3 MIU three times a week) + ribavirin (1,000/1,200 mg/day)	505
PegIntron monotherapy	PegIntron (0.5 microgram/kg/week)	315
	PegIntron (1.0 microgram/kg/week)	297
	PegIntron (1.5 micrograms/kg/week)	304

Table 5 Undesirable effects reported in clinical trials (≥ 10 % of patients in PegIntron + ribavirin group)			
	PegIntron + ribavirin	**Interferon alfa-2b + ribavirin**	**PegIntron monotherapy**
Application site disorder			
Injection site inflammation	20 %	17 %	39-44 %
Injection site reaction	54 %	36 %	7-9 %
Body as a whole			
Headache	58 %	57 %	57-63 %
Fatigue	56 %	59 %	43 %
Rigors	42 %	40 %	33-43 %
Fever	39 %	32 %	29-43 %
Flu-like symptoms	21 %	23 %	18-25 %
Asthenia	28 %	17 %	12-14 %
Weight decrease	30 %	19 %	8-18 %
Gastrointestinal			
Nausea	43 %	31 %	20-23 %
Anorexia	35 %	26 %	10-25 %
Diarrhoea	20 %	13 %	14-17 %
Abdominal pain	12 %	9 %	11 %
Vomiting	16 %	10 %	4-7 %
Musculoskeletal			
Myalgia	49 %	49 %	46-60 %
Arthralgia	31 %	26 %	23-28 %
Musculoskeletal pain	15 %	11 %	11-13 %
Psychiatric			
Depression	34 %	32 %	26 %
Irritability	32 %	34 %	19 %
Insomnia	37 %	41 %	16-19 %
Anxiety	14 %	14 %	8 %
Concentration impaired	18 %	21 %	9-10 %
Emotional lability	11 %	10 %	5 %
Respiratory system			
Pharyngitis	10 %	7 %	3 %
Coughing	14 %	11 %	4 %
Dyspnea	26 %	22 %	5 %
Skin and appendages			
Alopecia	45 %	32 %	20-34 %
Pruritus	27 %	27 %	7-9 %
Skin dry	23 %	21 %	6-9 %
Rash	21 %	21 %	5-7 %
Other			
Dizziness	17 %	16 %	7-12 %
Infection viral	10 %	5 %	4-5 %
Mouth dry	10 %	8 %	4-8 %

Table 6. Undesirable effects reported in clinical trials (1%-< 10% of patients treated with PegIntron + ribavirin or PegIntron monotherapy)		
Body system	**5-10%**	**1-<5%**
Body as a whole	chest pain, RUQ pain, malaise	erythema, injection site pain, flushing, thirst, herpes simplex, face or peripheral oedema, dehydration
Cardiovascular		tachycardia, palpitation, hypotension, hypertension, syncope
Central/peripheral nervous system	paresthesia	hypoaesthesia, hyperaesthesia, hypertonia, decreased libido, confusion, tremor, vertigo, migraine, tinnitus, hearing impairment/loss, ataxia, neuralgia
Endocrine	hypothyroidism,	hyperthyroidism, amenorrhoea, prostatitis, hyperuricemia, hypocalcemia
Gastrointestinal	dyspepsia,	constipation, taste perversion, loose stools, stomatitis, ulcerative stomatitis, gingival bleeding, glossitis, flatulence, hemorrhoids, gastroesophageal reflux, hepatomegaly, bilirubinemia, gingivitis
Haematologic	anaemia, leukopaenia	thrombocytopenia, lymphadenopathy,
Musculoskeletal		arthritis
Ocular		blurred vision, conjunctivitis, lacrimal gland disorder, eye pain
Psychiatric	agitation, nervousness	aggressive behaviour, somnolence, behavior disorder, apathy, appetite increased, sleep disorder, dreaming abnormal
Reproductive	menstrual disorder, menorrhagia	ovarian disorder, vaginal disorder, sexual dysfunction (not specified), impotence, breast pain
Respiratory		nonproductive cough, rhinitis, sinusitis, bronchitis, respiratory disorder, nasal congestion, rhinorrhea, dysphonia, epistaxis
Resistance mechanism		otitis media, fungal infection, bacterial infection
Skin and appendages	increased sweating	erythematous rash, eczema, photosensitivity reaction, maculopapular rash, abnormal hair texture, acne, dermatitis, furunculosis, nail disorder, psoriasis, urticaria
Urinary		micturition frequency, urine abnormal

Most cases of neutropaenia and thrombocytopaenia were mild (WHO grades 1 or 2). There were some cases of more severe neutropaenia in patients treated with the recommended doses of PegIntron in combination with ribavirin (WHO grade 3: 39 of 186 [21 %]; and WHO grade 4: 13 of 186 [7 %]).

In a clinical trial, approximately 1.2 % of patients treated with PegIntron or interferon alfa-2b in combination with ribavirin reported life-threatening psychiatric events during treatment. These events included suicidal ideation and attempted suicide (see section **4.4**). Following marketing, psychosis and hallucinations have been reported rarely.

Rarely reported events with interferon alfa-2b, including PegIntron, include seizure, pancreatitis, arrhythmia, peripheral neuropathy, diabetes, rhabdomyolysis, myositis, renal insufficiency and renal failure.

Cardiovascular (CVS) adverse events, particularly arrhythmia, appeared to be correlated mostly with pre-existing CVS disease and prior therapy with cardiotoxic agents (see section **4.4**). Cardiomyopathy, that may be reversible upon discontinuation of interferon alpha, has been reported rarely in patients without prior evidence of cardiac disease.

Very rarely cases of erythema multiforme, Stevens Johnson syndrome, toxic epidermal necrolysis, cardiac ischaemia, myocardial infarction, cerebrovascular ischaemia, cerebrovascular hemorrhage, encephalopathy, sarcoidosis or exacerbation of sarcoidosis, interstitial lung disease and injection site necrosis have been reported. Ulcerative and ischaemic colitis have been reported very rarely with PegIntron.

Very rarely, interferon alfa-2b or PegIntron used alone or in combination with ribavirin may be associated with aplastic anaemia.

Ophthalmological disorders that have been reported rarely with alpha interferons include retinopathies (including macular oedema), retinal haemorrhages, retinal artery or vein obstruction, cotton wool spots, loss of visual acuity or visual field, optic neuritis, and papilloedema (see section **4.4**).

A wide variety of autoimmune and immune-mediated disorders have been reported with alpha interferons including thyroid disorders, idiopathic and thrombotic thrombocytopenic purpura, vasculitis, neuropathies including mononeuropathies (see also section **4.4**, **Autoimmune disorders**).

4.9 Overdose

In clinical trials, cases of accidental overdose, at never more than twice the prescribed dose, were reported. There were no serious reactions. Undesirable effects resolved during continued administration of PegIntron.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunostimulants, Cytokines and immunomodulators, Interferons, Peginterferon alfa-2b, ATC code: L03A B10.

Recombinant interferon alfa-2b is covalently conjugated with monomethoxy polyethylene glycol at an average degree of substitution of 1 mole of polymer/mole of protein. The average molecular mass is approximately 31,300 daltons of which the protein moiety constitutes approximately 19,300.

Interferon alfa-2b
In vitro and *in vivo* studies suggest that the biological activity of PegIntron is derived from its interferon alfa-2b moiety.

Interferons exert their cellular activities by binding to specific membrane receptors on the cell surface. Studies with other interferons have demonstrated species specificity. However, certain monkey species, e.g., Rhesus monkeys, are susceptible to pharmacodynamic stimulation upon exposure to human type 1 interferons.

Once bound to the cell membrane, interferon initiates a complex sequence of intracellular events that include the induction of certain enzymes. It is thought that this process, at least in part, is responsible for the various cellular responses to interferon, including inhibition of virus replication in virus-infected cells, suppression of cell proliferation and such immunomodulating activities as enhancement

of the phagocytic activity of macrophages and augmentation of the specific cytotoxicity of lymphocytes for target cells. Any or all of these activities may contribute to interferon's therapeutic effects.

Recombinant interferon alfa-2b also inhibits viral replication *in vitro* and *in vivo*. Although the exact antiviral mode of action of recombinant interferon alfa-2b is unknown, it appears to alter the host cell metabolism. This action inhibits viral replication or if replication occurs, the progeny virions are unable to leave the cell.

PegIntron
PegIntron pharmacodynamics were assessed in a rising single-dose trial in healthy subjects by examining changes in oral temperature, concentrations of effector proteins such as serum neopterin and 2'5'-oligoadenylate synthetase (2'5'-OAS), as well as white cell and neutrophil counts. Subjects treated with PegIntron showed mild dose-related elevations in body temperature. Following single doses of PegIntron between 0.25 and 2.0 micrograms/kg/week, serum neopterin concentration was increased in a dose-related manner. Neutrophil and white cell count reductions at the end of week 4 correlated with the dose of PegIntron.

PegIntron clinical trials
Two pivotal trials have been conducted, one (C/I97-010) with PegIntron monotherapy; the other (C/I98-580) with PegIntron in combination with ribavirin. Eligible patients for these trials had chronic hepatitis C confirmed by a positive HCV-RNA polymerase chain reaction (PCR) assay (> 30 IU/ml), a liver biopsy consistent with a histological diagnosis of chronic hepatitis with no other cause for the chronic hepatitis, and abnormal serum ALT.

In the PegIntron monotherapy trial, a total of 916 naïve chronic hepatitis C patients were treated with PegIntron (0.5, 1.0 or 1.5 micrograms/kg/week) for one year with a follow-up period of six months. In addition, 303 patients received interferon alfa-2b (3 million International Units [MIU] three times a week as a comparator. This study showed that PegIntron was superior to interferon alfa-2b (**Table 7**).

In the PegIntron combination trial, 1,530 naïve patients were treated for one year with one of the following combination regimens:
- PegIntron (1.5 micrograms/kg/week) + ribavirin (800 mg/day), (n = 511).
- PegIntron (1.5 micrograms/kg/week for one month followed by 0.5 microgram/kg/week for 11 months) + ribavirin (1,000/1,200 mg/day), (n = 514).
- Interferon alfa-2b (3 MIU three times a week) + ribavirin (1,000/1,200 mg/day) (n = 505).

In this trial, the combination of PegIntron (1.5 micrograms/kg/week) and ribavirin was significantly more effective than the combination of interferon alfa-2b and ribavirin (**Table 7**), particularly in patients infected with Genotype 1 (**Table 8**). Sustained response was assessed by the response rate six months after the cessation of treatment.

HCV genotype and baseline virus load are prognostic factors which are known to affect response rates. However, response rates in this trial were shown to be dependent also on the dose of ribavirin administered in combination with PegIntron or interferon alfa-2b. In those patients that received > 10.6 mg/kg ribavirin (800 mg dose in typical 75 kg patient), regardless of genotype or viral load, response rates were significantly higher than in those patients that received ≤ 10.6 mg/kg ribavirin (**Table 8**), while response rates in patients that received > 13.2 mg/kg ribavirin were even higher.

Table 7 Sustained virological response (% patients HCV negative)

	PegIntron monotherapy				**PegIntron + ribavirin**		
Treatment regimen	**P 1.5**	**P 1.0**	**P 0.5**	**I**	**P 1.5/R**	**P 0.5/R**	**I/R**
Number of patients	304	297	315	303	511	514	505
Response at end of treatment	49 %	41 %	33 %	24 %	65 %	56 %	54 %

Sustained response	**23 %***	**25 %**	**18 %**	**12 %**	**54 %****	**47 %**	**47 %**

P 1.5 PegIntron 1.5 micrograms/kg
P 1.0 PegIntron 1.0 microgram/kg
P 0.5 PegIntron 0.5 microgram/kg
I Interferon alfa-2b 3 MIU
P 1.5/R PegIntron (1.5 micrograms/kg) + ribavirin (800 mg)
P 0.5/R PegIntron (1.5 to 0.5 microgram/kg) + ribavirin (1,000/1,200 mg)
I/R Interferon alfa-2b (3 MIU) + ribavirin (1,000/1,200 mg)
* $p < 0.001$ P 1.5 vs. I
** $p = 0.0143$ P 1.5/R vs. I/R

Table 8 Sustained response rates with PegIntron + ribavirin (by ribavirin dose, genotype and viral load)

HCV Genotype	Rebetol dose (mg/kg)	P 1.5/R	P 0.5/R	I/R
All Genotypes	**All**	**54 %**	**47 %**	**47 %**
	≤ 10.6	50 %	41 %	27 %
	> 10.6	61 %	48 %	47 %
Genotype 1	**All**	**42 %**	**34 %**	**33 %**
	≤ 10.6	38 %	25 %	20 %
	> 10.6	48 %	34 %	34 %
Genotype 1 ≤ 600,000 IU/ml	All	73 %	51 %	45 %
	≤ 10.6	74 %	25 %	33 %
	> 10.6	71 %	52 %	45 %
Genotype 1 > 600,000 IU/ml	All	30 %	27 %	29 %
	≤ 10.6	27 %	25 %	17 %
	> 10.6	37 %	27 %	29 %
Genotype 2/3	**All**	**82 %**	**80 %**	**79 %**
	≤ 10.6	79 %	73 %	50 %
	> 10.6	88 %	80 %	80 %

P 1.5/R PegIntron (1.5 micrograms/kg) + ribavirin (800 mg)
P 0.5/R PegIntron (1.5 to 0.5 microgram/kg) + ribavirin (1,000/1,200 mg)
I/R Interferon alfa-2b (3 MIU) + ribavirin (1,000/1,200 mg)

In the PegIntron monotherapy study, the Quality of Life was generally less affected by 0.5 microgram/kg of PegIntron than by either 1.0 microgram/kg of PegIntron once weekly or 3 MIU of interferon alfa-2b three times a week.

In a separate trial, 224 patients with genotype 2 or 3 received PegIntron, 1.5 microgram/kg subcutaneously, once weekly, in combination with ribavirin 800 mg –1,400 mg p.o. for 6 months (based on body weight, only three patients weighing > 105 kg, received the 1,400 mg dose, which has not yet been validated) (**Table 9**). Twenty-four % had bridging fibrosis or cirrhosis (Knodell 3/4).

Table 9. Virologic Response at End of Treatment, Sustained Virologic Response and Relapse by HCV Genotype and Viral Load*

	PegIntron 1.5 µg/kg Once Weekly Plus Rebetol 800-1400 mg/day		
	End of Treatment Response	Sustained Virologic Response	Relapse
All Subjects	94 % (211/224)	81 % (182/224)	12 % (27/224)
HCV 2	100 % (42/42)	93 % (39/42)	7 % (3/42)
≤ 600,000 IU/ml	100 % (20/20)	95 % (19/20)	5 % (1/20)
> 600,000 IU/mL	100 % (22/22)	91 % (20/22)	9 % (2/22)
HCV 3	93 % (169/182)	79 % (143/182)	14 %

			(24/166)
≤ 600,000 IU/ml	93 % (92/99)	86 % (85/99)	8 % (7/91)
> 600,000 IU/ml	93 % (77/83)	70 % (58/83)	23 % (17/75)

* Any subject with an undetectable HCV-RNA level at the Follow-Up Week 12 visit and missing data at the Follow-Up Week 24 visit was considered a sustained responder. Any subject with missing data in and after the Follow-Up Week 12 window was considered to be a non-responder at Week 24 of follow-up.

The 6 month treatment duration in this trial was better tolerated than one year of treatment in the pivotal combination trial; for discontinuation 5 % vs. 14 %, for dose modification 18 % vs. 49 %.

Predictability of sustained virological response
Virological reponse by week 12, defined as a 2-log viral load decrease or undetectable levels of HCV RNA has been shown to be predictive for sustained response (**Table 10**).

Table 10 Predictability of sustained response by viral response at week 12 and genotype*

Treatment	Genotype	Viral response at week 12	Sustained response	Negative predictive value
PegIntron 1.5 + ribavirin (> 10.6 mg/kg) 48-week treatment	1	Yes 75 % (82/110)	71 % (58/82)	----
		No 25 % (28/110)	0 % (0/28)	100 %
PegIntron 1.5 + ribavirin 800-1,400 mg 24-week treatment	2 and 3	Yes 99 % (213/215)	83 % (177/213)	----
		No 1 % (2/215)	50 % (1/2)	50 %

* reflects patients with 12 week data available

The negative predictive value for sustained response in patients treated with PegIntron in monotherapy was 98 %.

5.2 Pharmacokinetic properties

PegIntron is a well characterized polyethylene glycol-modified ("pegylated") derivative of interferon alfa-2b and is predominantly composed of monopegylated species. The plasma half-life of PegIntron is prolonged compared with non-pegylated interferon alfa-2b. PegIntron has a potential to depegylate to free interferon alfa-2b. The biologic activity of the pegylated isomers is qualitatively similar, but weaker than free interferon alfa-2b.

Following subcutaneous administration, maximal serum concentrations occur between 15-44 hours post-dose, and are sustained for up to 48-72 hours post-dose.

PegIntron C_{max} and AUC measurements increase in a dose-related manner. Mean apparent volume of distribution is 0.99 l/kg.

Upon multiple dosing, there is an accumulation of immunoreactive interferons. There is, however, only a modest increase in biologic activity as measured by a bioassay.

Mean (SD) PegIntron elimination half-life is approximately 40 hours (13.3 hours), with apparent clearance of 22.0 ml/hr·kg. The mechanisms involved in clearance of interferons in man have not yet been

fully elucidated. However, renal elimination may account for a minority (approximately 30 %) of PegIntron apparent clearance.

Renal function: Renal clearance appears to account for 30 % of total clearance of PegIntron. In a single dose study (1.0 microgram/kg) in patients with impaired renal function, C_{max}, AUC, and half-life increased in relation to the degree of renal impairment.

Based on these data, no dose modification is recommended based on creatinine clearance. However, because of marked intra-subject variability in interferon pharmacokinetics, it is recommended that patients be monitored closely during treatment with PegIntron (see section **4.2**). Patients with severe renal dysfunction or creatinine clearance < 50 ml/min must not be treated with PegIntron.

Hepatic function: The pharmacokinetics of PegIntron have not been evaluated in patients with severe hepatic dysfunction.

Elderly patients ≥ 65 years of age: The pharmacokinetics of PegIntron following a single subcutaneous dose of 1.0 microgram/kg were not affected by age. The data suggest that no alteration in PegIntron dosage is necessary based on advancing age.

Patients under the age of 18 years: Specific pharmacokinetic evaluations have not been performed on these patients. PegIntron is indicated for the treatment of chronic hepatitis C only in patients 18 years of age or older.

Interferon neutralising factors: Interferon neutralising factor assays were performed on serum samples of patients who received PegIntron in the clinical trial. Interferon neutralising factors are antibodies which neutralise the antiviral activity of interferon. The clinical incidence of neutralising factors in patients who received PegIntron 0.5 micrograms/kg is 1.1 %.

5.3 Preclinical safety data

PegIntron: Adverse events not observed in clinical trials were not seen in toxicity studies in monkeys. These studies were limited to four weeks due to the appearance of anti-interferon antibodies in most monkeys.

Reproduction studies of PegIntron have not been performed. Interferon alfa-2b has been shown to be an abortifacient in primates. PegIntron is likely to also cause this effect. Effects on fertility have not been determined. PegIntron showed no genotoxic potential. (see section **4.6** for relevant human data. It is not known whether the components of this medicinal product are excreted in human milk. Therefore, nursing must be discontinued prior to the initiation of therapy.)

The relative non-toxicity of monomethoxy-polyethylene glycol (mPEG), which is liberated from PegIntron by metabolism *in vivo* has been demonstrated in preclinical acute and subchronic toxicity studies in rodents and monkeys, standard embryo-foetal development studies and in *in vitro* mutagenicity assays.

PegIntron plus ribavirin: When used in combination with ribavirin, PegIntron did not cause any effects not previously seen with either active substance alone. The major treatment-related change was a reversible, mild to moderate anaemia, the severity of which was greater than that produced by either active substance alone.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder for solution for injection:

Disodium phosphate, anhydrous,

Sodium dihydrogen phosphate dihydrate,
Sucrose,
Polysorbate 80.
Solvent for parenteral use:
Water for injections.

Deliverable volume from pen = 0.5 ml. An overfill is also included for proper dispensing from the pen delivery system.

6.2 Incompatibilities

This medicinal product should only be reconstituted with the solvent provided and must not be mixed with other medicinal products (see also section **6.6**).

6.3 Shelf life

3 years

After reconstitution:
- Chemical and physical in-use stability has been demonstrated for 24 hours at 2°C - 8ºC.
- From a microbiological point of view, the product is to be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C - 8°C.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C). Do not freeze.

6.5 Nature and contents of container

The powder and solvent are both contained in a two-chamber cartridge, Type I flint glass, separated by a bromobutyl rubber plunger. The cartridge is sealed at one end with a polypropylene cap containing a bromobutyl rubber liner and at the other end by a bromobutyl rubber plunger.

PegIntron 80 micrograms is supplied as:
- 1 pen containing powder and solvent for solution for injection, 1 injection needle and 2 cleansing swabs;
- 4 pens containing powder and solvent for solution for injection, 4 injection needles and 8 cleansing swabs;
- 6 pens containing powder and solvent for solution for injection, 6 injection needles and 12 cleansing swabs;
- 12 pens containing powder and solvent for solution for injection, 12 injection needles and 24 cleansing swabs.

Not all pack sizes may be marketed.

6.6 Instructions for use and handling and disposal

PegIntron pre-filled pen contains a powder of peginterferon alfa-2b and a solvent for solution at a strength of 80 micrograms for single use. Each pen is reconstituted with the solvent provided in the two-chamber cartridge (water for injections) for administration of up to 0.5 ml of solution. A small volume is lost during preparation of PegIntron for injection when the dose is measured and injected. Therefore, each pen contains an excess amount of solvent and PegIntron powder to ensure delivery of the labelled dose in 0.5 ml of PegIntron, solution for injection. The reconstituted solution has a concentration of 80 micrograms in 0.5 ml.

PegIntron is injected subcutaneously after reconstituting the powder as instructed, attaching an injection

needle and setting the prescribed dose. A complete and illustrated set of instructions is provided in the Annex to the Package Leaflet.

Remove PegIntron pre-filled pen from the refrigerator before administration to allow the solvent to reach room temperature (not more than 25°C).

As for all parenteral medicinal products, inspect visually the reconstituted solution prior to administration. The reconstituted solution should be clear and colourless. Do not use if discolouration or particulate matter is present. After administering the dose, discard the PegIntron pre- filled pen and any unused solution contained in it.

7. MARKETING AUTHORISATION HOLDER

SP Europe
73, rue de Stalle
B-1180 Bruxelles
Belgium

8. MARKETING AUTHORISATION NUMBERS

EU/1/00/131/035
EU/1/00/131/036
EU/1/00/131/037
EU/1/00/131/038

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

6 February 2002

10. DATE OF REVISION OF THE TEXT

1. NAME OF THE MEDICINAL PRODUCT

PegIntron 100 micrograms, powder and solvent for solution for injection in pre-filled pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled pen of PegIntron 100 micrograms contains a sufficient amount of peginterferon alfa-2b as measured on a protein basis in a powder for solution for injection, and the corresponding amount of solvent, to provide 100 micrograms in 0.5 ml of peginterferon alfa-2b when reconstituted as recommended.

The active substance is a covalent conjugate of recombinant interferon alfa-2b* with monomethoxy polyethylene glycol. The potency of this product should not be compared to that of another pegylated or non-pegylated protein of the same therapeutic class. For more information, see section **5.1.**
*produced by rDNA technology in *E.coli* cells harbouring a genetically engineered plasmid hybrid encompassing an interferon alfa-2b gene from human leukocytes

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection
The white powder and the clear and colourless solvent are both contained in a two-chamber glass cartidge assembled into a single use pre-filled pen.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PegIntron is indicated for the treatment of adult patients with chronic hepatitis C who have elevated transaminases without liver decompensation and who are positive for serum HCV-RNA or anti-HCV (see section **4.4**).

The best way to use PegIntron in this indication is in combination with ribavirin.

This combination is indicated in naïve patients as well as in patients who have previously responded (with normalisation of ALT at the end of treatment) to interferon alpha monotherapy but who have subsequently relapsed.

Interferon monotherapy, including PegIntron, is indicated mainly in case of intolerance or contraindication to ribavirin.

Please refer also to the ribavirin Summary of Product Characteristics (SPC) when PegIntron is to be used in combination with ribavirin.

4.2 Posology and method of administration

Treatment should be initiated and monitored only by a physician experienced in the management of patients with hepatitis C.

Dose to be administered
PegIntron should be administered as a once weekly subcutaneous injection. The dose administered depends on whether it is used in combination with ribavirin or as monotherapy.

Combination therapy
PegIntron 1.5 micrograms/kg/week in combination with ribavirin capsules.

The intended dose of 1.5 μg/kg of PegIntron to be used in combination with ribavirin may be delivered in weight categories with the pen/vial strengths according to **Table 1**. Ribavirin capsules are to be administered orally each day in two divided doses with food (morning and evening).

Table 1 - Dosing for Combination Therapy

Body Weight (kg)	PegIntron		Ribavirin Capsules	
	Vial/Pen Strength (μg/0.5ml)	Administer Once Weekly (ml)	Total Daily Dose (mg)	Number of Capsules (200 mg)
< 40	50	0.5	800	4[a]
40-50	80	0.4	800	4[a]
51-64	80	0.5	800	4[a]
65-75	100	0.5	1,000	5[b]
76-85	120	0.5	1,000	5[b]
> 85	150	0.5	1,200	6[c]

a: 2 morning, 2 evening
b: 2 morning, 3 evening
c: 3 morning, 3 evening

Duration of treatment
Predictability of sustained virological response: Patients infected with virus genotype 1 who fail to achieve virological response at Week 12 are highly unlikely to become sustained virological responders (see also section **5.1**).

- **Genotype 1**: For patients who exhibit virological response at week 12, treatment should be continued for another nine month period (i.e., a total of 48 weeks).
- **Genotypes 2 or 3**: It is recommended that all patients be treated for 24 weeks.
- **Genotype 4:** In general, patients infected with genotype 4 are considered harder to treat and limited study data (n=66) indicate they are compatible with a posology as for genotype 1.

PegIntron monotherapy
As monotherapy the PegIntron regimen is 0.5 or 1.0 microgram/kg/week. The lowest vial or pen strength available is 50 μg/0.5 ml; therefore for patients prescribed 0.5 μg/kg/week, doses must be adjusted by volume as shown in **Table 2**. For the 1.0 μg/kg dose, similar volume adjustments can be made or alternate vial strengths can be used as shown in **Table 2**.

Table 2- Monotherapy Dosing

	0.5 μg/kg		1.0 μg/kg	
Body Weight (kg)	Vial/Pen Strength (μg/0.5ml)	Administer Once Weekly (ml)	Vial/Pen Strength (μg/0.5ml)	Administer Once Weekly (ml)
30-35	50*	0.15	50	0.3
36-45	50*	0.2	50	0.4
46-56	50*	0.25	50	0.5
57-72	50	0.3	80	0.4
73-88	50	0.4	80	0.5

89-106	50	0.5	100	0.5
> 106**	80	0.4	120	0.5
* Must use vial. Minimum delivery for pen is 0.3 ml. ** For patients > 120 kg, use 80 µg/0.5 ml vial				

Duration of treatment
For patients who exhibit virological response at Week 12, treatment should be continued for at least another three-month period (i.e., a total of six months). The decision to extend therapy to one year of treatment should be based on prognostic factors (e.g., genotype, age > 40 years, male gender, bridging fibrosis).

Dose modification for all patients
If severe adverse reactions or laboratory abnormalities develop during treatment with PegIntron monotherapy or PegIntron in combination with ribavirin, modify the dosages of each product as appropriate, until the adverse reactions abate. Guidelines were developed in clinical trials for dose modification.

Combination Therapy Dose Reduction Guidelines

Table 2a Dose modification guidelines for combination therapy (with ribavirin)

Laboratory values	**Reduce only ribavirin dose to 600 mg/day* if:**	**Reduce only PegIntron dose to one-half dose if:**	**Discontinue combination therapy if:**
Haemoglobin	< 10 g/dl	-	< 8.5 g/dl
Haemoglobin in: Patients with history of stable cardiac disease	≥ 2 g/dl decrease in haemoglobin during any four week period during treatment (permanent dose reduction)		< 12 g/dl after four weeks of dose reduction
White blood cells	-	< 1.5 x 10^9/l	< 1.0 x 10^9/l
Neutrophils	-	< 0.75 x 10^9/l	< 0.5 x 10^9/l
Platelets	-	< 50 x 10^9/l	< 25 x 10^9/l
Bilirubin – direct	-	-	2.5 x ULN**
Bilirubin – indirect	> 5 mg/dl	-	> 4 mg/dl (for > 4 weeks)
Creatinine	-	-	> 2.0 mg/dl
ALT/AST	-	-	2 x baseline and > 10 x ULN**

* Patients whose dose of ribavirin is reduced to 600 mg daily receive one 200 mg capsule in the morning and two 200 mg capsules in the evening.

** Upper limit of normal

Dose reduction of PegIntron may be accomplished by either reducing the prescribed volume by one-half or by utilizing a lower dose strength as shown in **Table 2b**.

Table 2b – Reduced PegIntron Dosing for Combination Therapy

Body Weight (kg)	**Target Reduced Dose (µg)**	**Vial/Pen Strength (µg/0.5 ml)**	**Administer Once Weekly (ml)**	**Amount Delivered (µg)**
< 40	25	50*	0.25	25
40-50	32	50	0.3	30
51-64	40	50	0.4	40
65-75	50	50	0.5	50

76-85	60	80	0.4	64
> 85	75	100	0.4	80
*Must use vial. Minimum delivery for pen is 0.3 ml.				

PegIntron Monotherapy Dose Reduction Guidelines

Dose modification guidelines for patients who use PegIntron monotherapy are shown in **Table 3a.**

Table 3a Dose modification guidelines for PegIntron monotherapy		
Laboratory values	**Reduce PegIntron to one-half dose if:**	**Discontinue PegIntron if:**
Neutrophils	< 0.75 x 10^9/l	< 0.5 x 10^9/l
Platelets	< 50 x 10^9/l	< 25 x 10^9/l

Dose reduction for patients who use 0.5 µg/kg PegIntron monotherapy must be accomplished by reducing the prescribed volume by one-half. The 50 µg/0.5 ml vial must be used if necessary since the pen can only deliver a minimum volume of 0.3 ml.

For patients who use 1.0 µg/kg PegIntron monotherapy, dose reduction may be accomplished by reducing the prescribed volume by one-half or by utilizing a lower dose strength as shown in **Table 3b**.

Table 3b – Reduced PegIntron Dose for the 1.0 µg/kg Monotherapy Regimen				
Body Weight (kg)	**Target Reduced Dose (µg)**	**Vial/Pen Strength (µg/0.5ml)**	**Administer Once Weekly (ml)**	**Amount Delivered (µg)**
30-35	15	50*	0.15	15
36-45	20	50*	0.20	20
46-56	25	50*	0.25	25
57-72	32	50	0.3	30
73-89	40	50	0.4	40
90-106	50	50	0.5	50
> 106	60	80	0.4	64
*Must use vial. Minimum delivery for pen is 0.3 ml.				

Special populations

Use in renal impairment: The clearance of PegIntron is reduced in patients with significant renal impairment. Patients with creatinine clearance ≤ 50 ml/minute must not be treated with PegIntron (see section **5.2**). It is recommended that patients with moderate renal impairment be closely monitored and that their weekly dose of PegIntron be reduced if medically appropriate.

Use in hepatic impairment: The safety and efficacy of PegIntron therapy has not been evaluated in patients with severe hepatic dysfunction, therefore PegIntron must not be used for these patients.

Use in the elderly (≥ 65 years of age): There are no apparent age-related effects on the pharmacokinetics of PegIntron. Data from elderly patients treated with a single dose of PegIntron suggest no alteration in PegIntron dose is necessary based on age (see section **5.2**).

Use in patients under the age of 18 years: PegIntron is not recommended for use in children or adolescents under the age of 18, as there is no experience in this group.

4.3 Contraindications

- Hypersensitivity to the active substance or to any interferon or to any of the excipients;
- Pregnant women;
- Women who are breast-feeding;
- A history of severe pre-existing cardiac disease, including unstable or uncontrolled cardiac disease in the previous six months (see section **4.4**);
- Severe, debilitating medical conditions, including patients with chronic renal failure or creatinine clearance < 50 ml/minute;
- Autoimmune hepatitis or a history of autoimmune disease;
- Severe hepatic dysfunction or decompensated cirrhosis of the liver;
- Pre-existing thyroid disease unless it can be controlled with conventional treatment;
- Epilepsy and/or compromised central nervous system (CNS) function.

4.4 Special warnings and special precautions for use

There is no experience with PegIntron in combination with ribavirin in patients who have relapsed after interferon alpha + ribavirin therapy.

All patients in the chronic hepatitis C studies had a liver biopsy before inclusion, but in certain cases (i.e. patients with genotype 2 and 3), treatment may be possible without histological confirmation. Current treatment guidelines should be consulted as to whether a liver biopsy is needed prior to commencing treatment.

Acute hypersensitivity: Acute hypersensitivity reactions (e.g., urticaria, angioedema, bronchoconstriction, anaphylaxis) have been observed rarely during interferon alfa-2b therapy. If such a reaction develops during treatment with PegIntron, discontinue treatment and institute appropriate medical therapy immediately. Transient rashes do not necessitate interruption of treatment.

Cardiovascular system: As with interferon alfa-2b, patients with a history of congestive heart failure, myocardial infarction and/or previous or current arrhythmic disorders, receiving PegIntron therapy require close monitoring. It is recommended that patients who have pre-existing cardiac abnormalities have electrocardiograms taken prior to and during the course of treatment. Cardiac arrhythmias (primarily supraventricular) usually respond to conventional therapy but may require discontinuation of PegIntron therapy.

Psychiatric and Central Nervous System (CNS): If treatment with peginterferon alfa-2b is judged necessary in patients with existence or history of severe psychiatric conditions, this should only be initiated after having ensured appropriate individualised diagnostic and therapeutic management of the psychiatric condition.
Severe CNS effects, particularly depression, suicidal ideation and attempted suicide have been observed in some patients during PegIntron therapy. Other CNS effects including aggressive behaviour, confusion and alterations of mental status have been observed with alpha interferon. If patients develop psychiatric or CNS problems, including clinical depression, it is recommended that the patient be carefully monitored due to the potential seriousness of these undesirable effects. If symptoms persist or worsen, discontinue PegIntron therapy.
More significant obtundation and coma, including cases of encephalopathy, have been observed in some patients, usually elderly, treated at higher doses for oncology indications. While these effects are generally reversible, in a few patients full resolution took up to three weeks. Very rarely, seizures have occurred with high doses of interferon alpha.

Liver function: As with all interferons, discontinue treatment with PegIntron in patients who develop prolongation of coagulation markers which might indicate liver decompensation.

Fever: While fever may be associated with the flu-like syndrome reported commonly during interferon therapy, other causes of persistent fever must be ruled out.

Hydration: Adequate hydration must be maintained in patients undergoing PegIntron therapy since hypotension related to fluid depletion has been seen in some patients treated with alpha interferons. Fluid replacement may be necessary.

Pulmonary changes: Pulmonary infiltrates, pneumonitis, and pneumonia, occasionally resulting in fatality, have been observed rarely in interferon alpha treated patients. Any patient developing fever, cough, dyspnea or other respiratory symptoms must have a chest X-ray taken. If the chest X-ray shows pulmonary infiltrates or there is evidence of pulmonary function impairment, the patient is to be monitored closely, and, if appropriate, discontinue interferon alpha. Prompt discontinuation of interferon alpha administration and treatment with corticosteroids appear to be associated with resolution of pulmonary adverse events.

Autoimmune disease: The development of auto-antibodies and autoimmune disorders has been reported during treatment with alpha interferons. Patients predisposed to the development of autoimmune disorders may be at increased risk. Patients with signs or symptoms compatible with autoimmune disorders should be evaluated carefully, and the benefit-risk of continued interferon therapy should be reassessed (see also section **4.4 Thyroid changes** and **4.8**).

Ocular changes: Ophthalmologic disorders, including retinal haemorrhages, cotton wool spots, and retinal artery or vein obstruction have been reported in rare instances after treatment with alpha interferons (see section **4.8**). All patients should have a baseline eye examination. Any patient complaining of ocular symptoms, including loss of visual acuity or visual field must have a prompt and complete eye examination. Periodic visual examinations are recommended during PegIntron therapy, particularly in patients with disorders that may be associated with retinopathy, such as diabetes mellitus or hypertension. Discontinuation of PegIntron should be considered in patients who develop new or worsening ophthalmological disorders.

Thyroid changes: Infrequently, patients treated for chronic hepatitis C with interferon alpha have developed thyroid abnormalities, either hypothyroidism or hyperthyroidism. Determine thyroid stimulating hormone (TSH) levels if, during the course of therapy, a patient develops symptoms consistent with possible thyroid dysfunction. In the presence of thyroid dysfunction, PegIntron treatment may be continued if TSH levels can be maintained in the normal range by medication.

Metabolic disturbances: Hypertriglyceridemia and aggravation of hypertriglyceridemia, sometimes severe, have been observed. Monitoring of lipid levels is, therefore, recommended.

HCV/HIV Coinfection
Patients co-infected with HIV and receiving Highly Active Anti-Retroviral Therapy (HAART) may be at increased risk of developing lactic acidosis. Caution should be used when adding PegIntron and ribavirin to HAART therapy (see ribavirin SPC).
Co-infected patients with advanced cirrhosis receiving HAART may be at increased risk of hepatic decompensation and death. Adding treatment with alfa interferons alone or in combination with ribavirin may increase the risk in this patient subset.

Organ transplant recipients: The safety and efficacy of PegIntron alone or in combination with ribavirin for the treatment of hepatitis C in liver or other organ transplant recipients have not been studied. Preliminary data indicates that interferon alpha therapy may be associated with an increased rate of kidney graft rejection. Liver graft rejection has also been reported.

Other: Due to reports of interferon alpha exacerbating pre-existing psoriatic disease and sarcoidosis, use

of PegIntron in patients with psoriasis or sarcoidosis is recommended only if the potential benefit justifies the potential risk.

Laboratory tests: Standard haematologic tests, blood chemistry and a test of thyroid function must be conducted in all patients prior to initiating therapy. Acceptable baseline values that may be considered as a guideline prior to initiation of PegIntron therapy are:

- Platelets ≥ 100,000/mm^3
- Neutrophil count ≥ 1,500/mm^3
- TSH level must be within normal limits

Laboratory evaluations are to be conducted at weeks 2 and 4 of therapy, and periodically thereafter as clinically appropriate.

4.5 Interaction with other medicinal products and other forms of interaction

Results of a single-dose study with PegIntron demonstrated no effect on the activity of cytochrome (CY) P1A2, CYP2C8/9, CYP2D6, and hepatic CYP3A4 or N-acetyl transferase. Caution should be advised in the interpretation of these results as the use of other forms of interferon alpha result in a 50 % reduction in the clearance and thus a doubling of plasma concentrations of theophylline, a substrate of CYP1A2.

No pharmacokinetic interactions were noted between PegIntron and ribavirin in a multiple-dose pharmacokinetic study.

4.6 Pregnancy and lactation

There are no adequate data on the use of interferon alfa-2b in pregnant women. Interferon alfa-2b has been shown to be abortifacient in primates. PegIntron is likely to also cause this effect. PegIntron should not be used during pregnancy (see section **5.3**).

PegIntron is recommended for use in fertile women only when they are using effective contraception during the treatment period.

Lactation: It is not known whether the components of this medicinal product are excreted in human milk. Because of the potential for adverse reactions in nursing infants, nursing must be discontinued prior to initiation of treatment.

Ribavirin is teratogenic and embryocidal and must not be used in pregnant women (see ribavirin SPC, **5.3**).

4.7 Effects on ability to drive and use machines

Patients who develop fatigue, somnolence or confusion during treatment with PegIntron are cautioned to avoid driving or operating machinery.

4.8 Undesirable effects

The safety of PegIntron is evaluated from data from two clinical trials: one with PegIntron monotherapy, one with PegIntron in combination with ribavirin. In both cases, patients were treated for one year.

Table 4 describes the regimens and patient exposure for one year of treatment in patients with no previous exposure to interferon (interferon-naïve patients). Because of a significant overlap in the pattern of undesirable effects with PegIntron monotherapy, groups of patients have been brought together in **Table 5** to show the pattern of reported effects for all monotherapy groups.

Table 4	Regimens and patient exposure	
Treatment	**Regimen**	**Number of patients treated for one year**
PegIntron + ribavirin	PegIntron (1.5 micrograms/kg/week) + ribavirin (> 10.6 mg/kg/day)	188
Interferon alfa-2b + ribavirin	Interferon alfa-2b (3 MIU three times a week) + ribavirin (1,000/1,200 mg/day)	505
PegIntron monotherapy	PegIntron (0.5 microgram/kg/week)	315
	PegIntron (1.0 microgram/kg/week)	297
	PegIntron (1.5 micrograms/kg/week)	304

Table 5 Undesirable effects reported in clinical trials (≥ 10 % of patients in PegIntron + ribavirin group)			
	PegIntron + ribavirin	**Interferon alfa-2b + ribavirin**	**PegIntron monotherapy**
Application site disorder			
Injection site inflammation	20 %	17 %	39-44 %
Injection site reaction	54 %	36 %	7-9 %
Body as a whole			
Headache	58 %	57 %	57-63 %
Fatigue	56 %	59 %	43 %
Rigors	42 %	40 %	33-43 %
Fever	39 %	32 %	29-43 %
Flu-like symptoms	21 %	23 %	18-25 %
Asthenia	28 %	17 %	12-14 %
Weight decrease	30 %	19 %	8-18 %
Gastrointestinal			
Nausea	43 %	31 %	20-23 %
Anorexia	35 %	26 %	10-25 %
Diarrhoea	20 %	13 %	14-17 %
Abdominal pain	12 %	9 %	11 %
Vomiting	16 %	10 %	4-7 %
Musculoskeletal			
Myalgia	49 %	49 %	46-60 %
Arthralgia	31 %	26 %	23-28 %
Musculoskeletal pain	15 %	11 %	11-13 %
Psychiatric			
Depression	34 %	32 %	26 %
Irritability	32 %	34 %	19 %
Insomnia	37 %	41 %	16-19 %
Anxiety	14 %	14 %	8 %
Concentration impaired	18 %	21 %	9-10 %
Emotional lability	11 %	10 %	5 %
Respiratory system			
Pharyngitis	10 %	7 %	3 %
Coughing	14 %	11 %	4 %
Dyspnea	26 %	22 %	5 %
Skin and appendages			
Alopecia	45 %	32 %	20-34 %
Pruritus	27 %	27 %	7-9 %
Skin dry	23 %	21 %	6-9 %
Rash	21 %	21 %	5-7 %
Other			
Dizziness	17 %	16 %	7-12 %
Infection viral	10 %	5 %	4-5 %
Mouth dry	10 %	8 %	4-8 %

Table 6. Undesirable effects reported in clinical trials (1%-< 10% of patients treated with PegIntron + ribavirin or PegIntron monotherapy)		
Body system	**5-10%**	**1-<5%**
Body as a whole	chest pain, RUQ pain, malaise	erythema, injection site pain, flushing, thirst, herpes simplex, face or peripheral oedema, dehydration
Cardiovascular		tachycardia, palpitation, hypotension, hypertension, syncope
Central/peripheral nervous system	paresthesia	hypoaesthesia, hyperaesthesia, hypertonia, decreased libido, confusion, tremor, vertigo, migraine, tinnitus, hearing impairment/loss, ataxia, neuralgia
Endocrine	hypothyroidism,	hyperthyroidism, amenorrhoea, prostatitis, hyperuricemia, hypocalcemia
Gastrointestinal	dyspepsia,	constipation, taste perversion, loose stools, stomatitis, ulcerative stomatitis, gingival bleeding, glossitis, flatulence, hemorrhoids, gastroesophageal reflux, hepatomegaly, bilirubinemia, gingivitis
Haematologic	anaemia, leukopaenia	thrombocytopenia, lymphadenopathy,
Musculoskeletal		arthritis
Ocular		blurred vision, conjunctivitis, lacrimal gland disorder, eye pain
Psychiatric	agitation, nervousness	aggressive behaviour, somnolence, behavior disorder, apathy, appetite increased, sleep disorder, dreaming abnormal
Reproductive	menstrual disorder, menorrhagia	ovarian disorder, vaginal disorder, sexual dysfunction (not specified), impotence, breast pain
Respiratory		nonproductive cough, rhinitis, sinusitis, bronchitis, respiratory disorder, nasal congestion, rhinorrhea, dysphonia, epistaxis
Resistance mechanism		otitis media, fungal infection, bacterial infection
Skin and appendages	increased sweating	erythematous rash, eczema, photosensitivity reaction, maculopapular rash, abnormal hair texture, acne, dermatitis, furunculosis, nail disorder, psoriasis, urticaria
Urinary		micturition frequency, urine abnormal

Most cases of neutropaenia and thrombocytopaenia were mild (WHO grades 1 or 2). There were some cases of more severe neutropaenia in patients treated with the recommended doses of PegIntron in combination with ribavirin (WHO grade 3: 39 of 186 [21 %]; and WHO grade 4: 13 of 186 [7 %]).

In a clinical trial, approximately 1.2 % of patients treated with PegIntron or interferon alfa-2b in combination with ribavirin reported life-threatening psychiatric events during treatment. These events included suicidal ideation and attempted suicide (see section **4.4**). Following marketing, psychosis and hallucinations have been reported rarely.

Rarely reported events with interferon alfa-2b, including PegIntron, include seizure, pancreatitis, arrhythmia, peripheral neuropathy, diabetes, rhabdomyolysis, myositis, renal insufficiency and renal failure.

Cardiovascular (CVS) adverse events, particularly arrhythmia, appeared to be correlated mostly with pre-existing CVS disease and prior therapy with cardiotoxic agents (see section **4.4**). Cardiomyopathy, that may be reversible upon discontinuation of interferon alpha, has been reported rarely in patients without prior evidence of cardiac disease.

Very rarely cases of erythema multiforme, Stevens Johnson syndrome, toxic epidermal necrolysis, cardiac ischaemia, myocardial infarction, cerebrovascular ischaemia, cerebrovascular hemorrhage, encephalopathy, sarcoidosis or exacerbation of sarcoidosis, interstitial lung disease and injection site necrosis have been reported. Ulcerative and ischaemic colitis have been reported very rarely with PegIntron.

Very rarely, interferon alfa-2b or PegIntron used alone or in combination with ribavirin may be associated with aplastic anaemia.

Ophthalmological disorders that have been reported rarely with alpha interferons include retinopathies (including macular oedema), retinal haemorrhages, retinal artery or vein obstruction, cotton wool spots, loss of visual acuity or visual field, optic neuritis, and papilloedema (see section **4.4**).

A wide variety of autoimmune and immune-mediated disorders have been reported with alpha interferons including thyroid disorders, idiopathic and thrombotic thrombocytopenic purpura, vasculitis, neuropathies including mononeuropathies (see also section **4.4**, **Autoimmune disorders**).

4.9 Overdose

In clinical trials, cases of accidental overdose, at never more than twice the prescribed dose, were reported. There were no serious reactions. Undesirable effects resolved during continued administration of PegIntron.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunostimulants, Cytokines and immunomodulators, Interferons, Peginterferon alfa-2b, ATC code: L03A B10.

Recombinant interferon alfa-2b is covalently conjugated with monomethoxy polyethylene glycol at an average degree of substitution of 1 mole of polymer/mole of protein. The average molecular mass is approximately 31,300 daltons of which the protein moiety constitutes approximately 19,300.

Interferon alfa-2b
In vitro and *in vivo* studies suggest that the biological activity of PegIntron is derived from its interferon alfa-2b moiety.

Interferons exert their cellular activities by binding to specific membrane receptors on the cell surface. Studies with other interferons have demonstrated species specificity. However, certain monkey species, e.g., Rhesus monkeys, are susceptible to pharmacodynamic stimulation upon exposure to human type 1 interferons.

Once bound to the cell membrane, interferon initiates a complex sequence of intracellular events that include the induction of certain enzymes. It is thought that this process, at least in part, is responsible for the various cellular responses to interferon, including inhibition of virus replication in virus-infected cells, suppression of cell proliferation and such immunomodulating activities as enhancement

of the phagocytic activity of macrophages and augmentation of the specific cytotoxicity of lymphocytes for target cells. Any or all of these activities may contribute to interferon's therapeutic effects.

Recombinant interferon alfa-2b also inhibits viral replication *in vitro* and *in vivo*. Although the exact antiviral mode of action of recombinant interferon alfa-2b is unknown, it appears to alter the host cell metabolism. This action inhibits viral replication or if replication occurs, the progeny virions are unable to leave the cell.

PegIntron
PegIntron pharmacodynamics were assessed in a rising single-dose trial in healthy subjects by examining changes in oral temperature, concentrations of effector proteins such as serum neopterin and 2'5'-oligoadenylate synthetase (2'5'-OAS), as well as white cell and neutrophil counts. Subjects treated with PegIntron showed mild dose-related elevations in body temperature. Following single doses of PegIntron between 0.25 and 2.0 micrograms/kg/week, serum neopterin concentration was increased in a dose-related manner. Neutrophil and white cell count reductions at the end of week 4 correlated with the dose of PegIntron.

PegIntron clinical trials
Two pivotal trials have been conducted, one (C/I97-010) with PegIntron monotherapy; the other (C/I98-580) with PegIntron in combination with ribavirin. Eligible patients for these trials had chronic hepatitis C confirmed by a positive HCV-RNA polymerase chain reaction (PCR) assay (> 30 IU/ml), a liver biopsy consistent with a histological diagnosis of chronic hepatitis with no other cause for the chronic hepatitis, and abnormal serum ALT.

In the PegIntron monotherapy trial, a total of 916 naïve chronic hepatitis C patients were treated with PegIntron (0.5, 1.0 or 1.5 micrograms/kg/week) for one year with a follow-up period of six months. In addition, 303 patients received interferon alfa-2b (3 million International Units [MIU] three times a week as a comparator. This study showed that PegIntron was superior to interferon alfa-2b (**Table 7**).

In the PegIntron combination trial, 1,530 naïve patients were treated for one year with one of the following combination regimens:
- PegIntron (1.5 micrograms/kg/week) + ribavirin (800 mg/day), (n = 511).
- PegIntron (1.5 micrograms/kg/week for one month followed by 0.5 microgram/kg/week for 11 months) + ribavirin (1,000/1,200 mg/day), (n = 514).
- Interferon alfa-2b (3 MIU three times a week) + ribavirin (1,000/1,200 mg/day) (n = 505).

In this trial, the combination of PegIntron (1.5 micrograms/kg/week) and ribavirin was significantly more effective than the combination of interferon alfa-2b and ribavirin (**Table 7**), particularly in patients infected with Genotype 1 (**Table 8**). Sustained response was assessed by the response rate six months after the cessation of treatment.

HCV genotype and baseline virus load are prognostic factors which are known to affect response rates. However, response rates in this trial were shown to be dependent also on the dose of ribavirin administered in combination with PegIntron or interferon alfa-2b. In those patients that received > 10.6 mg/kg ribavirin (800 mg dose in typical 75 kg patient), regardless of genotype or viral load, response rates were significantly higher than in those patients that received ≤ 10.6 mg/kg ribavirin (**Table 8**), while response rates in patients that received > 13.2 mg/kg ribavirin were even higher.

Table 7 Sustained virological response (% patients HCV negative)

	PegIntron monotherapy				**PegIntron + ribavirin**		
Treatment regimen	**P 1.5**	**P 1.0**	**P 0.5**	**I**	**P 1.5/R**	**P 0.5/R**	**I/R**
Number of patients	304	297	315	303	511	514	505
Response at end of treatment	49 %	41 %	33 %	24 %	65 %	56 %	54 %

Sustained response	**23 %***	**25 %**	**18 %**	**12 %**	**54 %****	**47 %**	**47 %**

P 1.5 PegIntron 1.5 micrograms/kg
P 1.0 PegIntron 1.0 microgram/kg
P 0.5 PegIntron 0.5 microgram/kg
I Interferon alfa-2b 3 MIU
P 1.5/R PegIntron (1.5 micrograms/kg) + ribavirin (800 mg)
P 0.5/R PegIntron (1.5 to 0.5 microgram/kg) + ribavirin (1,000/1,200 mg)
I/R Interferon alfa-2b (3 MIU) + ribavirin (1,000/1,200 mg)
* $p < 0.001$ P 1.5 vs. I
** $p = 0.0143$ P 1.5/R vs. I/R

Table 8 Sustained response rates with PegIntron + ribavirin (by ribavirin dose, genotype and viral load)

HCV Genotype	Rebetol dose (mg/kg)	P 1.5/R	P 0.5/R	I/R
All Genotypes	**All**	**54 %**	**47 %**	**47 %**
	≤ 10.6	50 %	41 %	27 %
	> 10.6	61 %	48 %	47 %
Genotype 1	**All**	**42 %**	**34 %**	**33 %**
	≤ 10.6	38 %	25 %	20 %
	> 10.6	48 %	34 %	34 %
Genotype 1 ≤ 600,000 IU/ml	All	73 %	51 %	45 %
	≤ 10.6	74 %	25 %	33 %
	> 10.6	71 %	52 %	45 %
Genotype 1 > 600,000 IU/ml	All	30 %	27 %	29 %
	≤ 10.6	27 %	25 %	17 %
	> 10.6	37 %	27 %	29 %
Genotype 2/3	**All**	**82 %**	**80 %**	**79 %**
	≤ 10.6	79 %	73 %	50 %
	> 10.6	88 %	80 %	80 %

P 1.5/R PegIntron (1.5 micrograms/kg) + ribavirin (800 mg)
P 0.5/R PegIntron (1.5 to 0.5 microgram/kg) + ribavirin (1,000/1,200 mg)
I/R Interferon alfa-2b (3 MIU) + ribavirin (1,000/1,200 mg)

In the PegIntron monotherapy study, the Quality of Life was generally less affected by 0.5 microgram/kg of PegIntron than by either 1.0 microgram/kg of PegIntron once weekly or 3 MIU of interferon alfa-2b three times a week.

In a separate trial, 224 patients with genotype 2 or 3 received PegIntron, 1.5 microgram/kg subcutaneously, once weekly, in combination with ribavirin 800 mg –1,400 mg p.o. for 6 months (based on body weight, only three patients weighing > 105 kg, received the 1,400 mg dose, which has not yet been validated) (**Table 9**). Twenty-four % had bridging fibrosis or cirrhosis (Knodell 3/4).

Table 9. Virologic Response at End of Treatment, Sustained Virologic Response and Relapse by HCV Genotype and Viral Load*

	PegIntron 1.5 µg/kg Once Weekly Plus Rebetol 800-1400 mg/day		
	End of Treatment Response	Sustained Virologic Response	Relapse
All Subjects	94 % (211/224)	81 % (182/224)	12 % (27/224)
HCV 2	100 % (42/42)	93 % (39/42)	7 % (3/42)
≤ 600,000 IU/ml	100 % (20/20)	95 % (19/20)	5 % (1/20)
> 600,000 IU/mL	100 % (22/22)	91 % (20/22)	9 % (2/22)
HCV 3	93 % (169/182)	79 % (143/182)	14 %

			(24/166)
≤ 600,000 IU/ml	93 % (92/99)	86 % (85/99)	8 % (7/91)
> 600,000 IU/ml	93 % (77/83)	70 % (58/83)	23 % (17/75)

* Any subject with an undetectable HCV-RNA level at the Follow-Up Week 12 visit and missing data at the Follow-Up Week 24 visit was considered a sustained responder. Any subject with missing data in and after the Follow-Up Week 12 window was considered to be a non-responder at Week 24 of follow-up.

The 6 month treatment duration in this trial was better tolerated than one year of treatment in the pivotal combination trial; for discontinuation 5 % vs. 14 %, for dose modification 18 % vs. 49 %.

Predictability of sustained virological response
Virological reponse by week 12, defined as a 2-log viral load decrease or undetectable levels of HCV RNA has been shown to be predictive for sustained response (**Table 10**).

Table 10 Predictability of sustained response by viral response at week 12 and genotype*

Treatment	Genotype	Viral response at week 12	Sustained response	Negative predictive value
PegIntron 1.5 + ribavirin (> 10.6 mg/kg) 48-week treatment	1	Yes 75 % (82/110)	71 % (58/82)	----
		No 25 % (28/110)	0 % (0/28)	100 %
PegIntron 1.5 + ribavirin 800-1,400 mg 24-week treatment	2 and 3	Yes 99 % (213/215)	83 % (177/213)	----
		No 1 % (2/215)	50 % (1/2)	50 %

* reflects patients with 12 week data available

The negative predictive value for sustained response in patients treated with PegIntron in monotherapy was 98 %.

5.2 Pharmacokinetic properties

PegIntron is a well characterized polyethylene glycol-modified ("pegylated") derivative of interferon alfa-2b and is predominantly composed of monopegylated species. The plasma half-life of PegIntron is prolonged compared with non-pegylated interferon alfa-2b. PegIntron has a potential to depegylate to free interferon alfa-2b. The biologic activity of the pegylated isomers is qualitatively similar, but weaker than free interferon alfa-2b.

Following subcutaneous administration, maximal serum concentrations occur between 15-44 hours post-dose, and are sustained for up to 48-72 hours post-dose.

PegIntron C_{max} and AUC measurements increase in a dose-related manner. Mean apparent volume of distribution is 0.99 l/kg.

Upon multiple dosing, there is an accumulation of immunoreactive interferons. There is, however, only a modest increase in biologic activity as measured by a bioassay.

Mean (SD) PegIntron elimination half-life is approximately 40 hours (13.3 hours), with apparent clearance of 22.0 ml/hr·kg. The mechanisms involved in clearance of interferons in man have not yet been fully elucidated. However, renal elimination may account for a minority (approximately 30 %) of PegIntron apparent clearance.

Renal function: Renal clearance appears to account for 30 % of total clearance of PegIntron. In a single dose study (1.0 microgram/kg) in patients with impaired renal function, C_{max}, AUC, and half-life increased in relation to the degree of renal impairment.

Based on these data, no dose modification is recommended based on creatinine clearance. However, because of marked intra-subject variability in interferon pharmacokinetics, it is recommended that patients be monitored closely during treatment with PegIntron (see section **4.2**). Patients with severe renal dysfunction or creatinine clearance < 50 ml/min must not be treated with PegIntron.

Hepatic function: The pharmacokinetics of PegIntron have not been evaluated in patients with severe hepatic dysfunction.

Elderly patients ≥ 65 years of age: The pharmacokinetics of PegIntron following a single subcutaneous dose of 1.0 microgram/kg were not affected by age. The data suggest that no alteration in PegIntron dosage is necessary based on advancing age.

Patients under the age of 18 years: Specific pharmacokinetic evaluations have not been performed on these patients. PegIntron is indicated for the treatment of chronic hepatitis C only in patients 18 years of age or older.

Interferon neutralising factors: Interferon neutralising factor assays were performed on serum samples of patients who received PegIntron in the clinical trial. Interferon neutralising factors are antibodies which neutralise the antiviral activity of interferon. The clinical incidence of neutralising factors in patients who received PegIntron 0.5 micrograms/kg is 1.1 %.

5.3 Preclinical safety data

PegIntron: Adverse events not observed in clinical trials were not seen in toxicity studies in monkeys. These studies were limited to four weeks due to the appearance of anti-interferon antibodies in most monkeys.

Reproduction studies of PegIntron have not been performed. Interferon alfa-2b has been shown to be an abortifacient in primates. PegIntron is likely to also cause this effect. Effects on fertility have not been determined. PegIntron showed no genotoxic potential. (see section **4.6** for relevant human data. It is not known whether the components of this medicinal product are excreted in human milk. Therefore, nursing must be discontinued prior to the initiation of therapy.)

The relative non-toxicity of monomethoxy-polyethylene glycol (mPEG), which is liberated from PegIntron by metabolism *in vivo* has been demonstrated in preclinical acute and subchronic toxicity studies in rodents and monkeys, standard embryo-foetal development studies and in *in vitro* mutagenicity assays.

PegIntron plus ribavirin: When used in combination with ribavirin, PegIntron did not cause any effects not previously seen with either active substance alone. The major treatment-related change was a reversible, mild to moderate anaemia, the severity of which was greater than that produced by either active substance alone.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder for solution for injection:

Disodium phosphate, anhydrous,
Sodium dihydrogen phosphate dihydrate,
Sucrose,

Polysorbate 80.
Solvent for parenteral use:
Water for injections.

Deliverable volume from pen = 0.5 ml. An overfill is also included for proper dispensing from the pen delivery system.

6.2 Incompatibilities

This medicinal product should only be reconstituted with the solvent provided and must not be mixed with other medicinal products (see also section **6.6**).

6.3 Shelf life

3 years

After reconstitution:
- Chemical and physical in-use stability has been demonstrated for 24 hours at 2°C - 8ºC.
- From a microbiological point of view, the product is to be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C - 8°C.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C). Do not freeze.

6.5 Nature and contents of container

The powder and solvent are both contained in a two-chamber cartridge, Type I flint glass, separated by a bromobutyl rubber plunger. The cartridge is sealed at one end with a polypropylene cap containing a bromobutyl rubber liner and at the other end by a bromobutyl rubber plunger.

PegIntron 100 micrograms is supplied as:
- 1 pen containing powder and solvent for solution for injection, 1 injection needle and 2 cleansing swabs;
- 4 pens containing powder and solvent for solution for injection, 4 injection needles and 8 cleansing swabs;
- 6 pens containing powder and solvent for solution for injection, 6 injection needles and 12 cleansing swabs;
- 12 pens containing powder and solvent for solution for injection, 12 injection needles and 24 cleansing swabs.

Not all pack sizes may be marketed.

6.6 Instructions for use and handling and disposal

PegIntron pre-filled pen contains a powder of peginterferon alfa-2b and a solvent for solution at a strength of 100 micrograms for single use. Each pen is reconstituted with the solvent provided in the two-chamber cartridge (water for injections) for administration of up to 0.5 ml of solution. A small volume is lost during preparation of PegIntron for injection when the dose is measured and injected. Therefore, each pen contains an excess amount of solvent and PegIntron powder to ensure delivery of the labelled dose in 0.5 ml of PegIntron, solution for injection. The reconstituted solution has a concentration of 100 micrograms in 0.5 ml.

PegIntron is injected subcutaneously after reconstituting the powder as instructed, attaching an injection needle and setting the prescribed dose. A complete and illustrated set of instructions is provided in the Annex to the Package Leaflet.

Remove PegIntron pre-filled pen from the refrigerator before administration to allow the solvent to reach room temperature (not more than 25°C).

As for all parenteral medicinal products, inspect visually the reconstituted solution prior to administration. The reconstituted solution should be clear and colourless. Do not use if discolouration or particulate matter is present. After administering the dose, discard the PegIntron pre- filled pen and any unused solution contained in it.

7. MARKETING AUTHORISATION HOLDER

SP Europe
73, rue de Stalle
B-1180 Bruxelles
Belgium

8. MARKETING AUTHORISATION NUMBERS

EU/1/00/131/039
EU/1/00/131/040
EU/1/00/131/041
EU/1/00/131/042

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

6 February 2002

10. DATE OF REVISION OF THE TEXT

1. NAME OF THE MEDICINAL PRODUCT

PegIntron 120 micrograms, powder and solvent for solution for injection in pre-filled pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled pen of PegIntron 120 micrograms contains a sufficient amount of peginterferon alfa-2b as measured on a protein basis in a powder for solution for injection, and the corresponding amount of solvent, to provide 120 micrograms in 0.5 ml of peginterferon alfa-2b when reconstituted as recommended.

The active substance is a covalent conjugate of recombinant interferon alfa-2b* with monomethoxy polyethylene glycol. The potency of this product should not be compared to that of another pegylated or non-pegylated protein of the same therapeutic class. For more information, see section **5.1.**
*produced by rDNA technology in *E.coli* cells harbouring a genetically engineered plasmid hybrid encompassing an interferon alfa-2b gene from human leukocytes

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection
The white powder and the clear and colourless solvent are both contained in a two-chamber glass cartidge assembled into a single use pre-filled pen.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PegIntron is indicated for the treatment of adult patients with chronic hepatitis C who have elevated transaminases without liver decompensation and who are positive for serum HCV-RNA or anti-HCV (see section **4.4**).

The best way to use PegIntron in this indication is in combination with ribavirin.

This combination is indicated in naïve patients as well as in patients who have previously responded (with normalisation of ALT at the end of treatment) to interferon alpha monotherapy but who have subsequently relapsed.

Interferon monotherapy, including PegIntron, is indicated mainly in case of intolerance or contraindication to ribavirin.

Please refer also to the ribavirin Summary of Product Characteristics (SPC) when PegIntron is to be used in combination with ribavirin.

4.2 Posology and method of administration

Treatment should be initiated and monitored only by a physician experienced in the management of patients with hepatitis C.

Dose to be administered
PegIntron should be administered as a once weekly subcutaneous injection. The dose administered depends on whether it is used in combination with ribavirin or as monotherapy.

Combination therapy
PegIntron 1.5 micrograms/kg/week in combination with ribavirin capsules.

The intended dose of 1.5 μg/kg of PegIntron to be used in combination with ribavirin may be delivered in weight categories with the pen/vial strengths according to **Table 1**. Ribavirin capsules are to be administered orally each day in two divided doses with food (morning and evening).

Table 1 - Dosing for Combination Therapy

Body Weight (kg)	PegIntron		Ribavirin Capsules	
	Vial/Pen Strength (μg/0.5ml)	Administer Once Weekly (ml)	Total Daily Dose (mg)	Number of Capsules (200 mg)
< 40	50	0.5	800	4[a]
40-50	80	0.4	800	4[a]
51-64	80	0.5	800	4[a]
65-75	100	0.5	1,000	5[b]
76-85	120	0.5	1,000	5[b]
> 85	150	0.5	1,200	6[c]

a: 2 morning, 2 evening
b: 2 morning, 3 evening
c: 3 morning, 3 evening

Duration of treatment
Predictability of sustained virological response: Patients infected with virus genotype 1 who fail to achieve virological response at Week 12 are highly unlikely to become sustained virological responders (see also section **5.1**).

- **Genotype 1**: For patients who exhibit virological response at week 12, treatment should be continued for another nine month period (i.e., a total of 48 weeks).
- **Genotypes 2 or 3**: It is recommended that all patients be treated for 24 weeks.
- **Genotype 4:** In general, patients infected with genotype 4 are considered harder to treat and limited study data (n=66) indicate they are compatible with a posology as for genotype 1.

PegIntron monotherapy
As monotherapy the PegIntron regimen is 0.5 or 1.0 microgram/kg/week. The lowest vial or pen strength available is 50 μg/0.5 ml; therefore for patients prescribed 0.5 μg/kg/week, doses must be adjusted by volume as shown in **Table 2**. For the 1.0 μg/kg dose, similar volume adjustments can be made or alternate vial strengths can be used as shown in **Table 2**.

Table 2- Monotherapy Dosing

	0.5 μg/kg		1.0 μg/kg	
Body Weight (kg)	Vial/Pen Strength (μg/0.5ml)	Administer Once Weekly (ml)	Vial/Pen Strength (μg/0.5ml)	Administer Once Weekly (ml)
30-35	50*	0.15	50	0.3
36-45	50*	0.2	50	0.4
46-56	50*	0.25	50	0.5
57-72	50	0.3	80	0.4
73-88	50	0.4	80	0.5

89-106	50	0.5	100	0.5
> 106**	80	0.4	120	0.5
* Must use vial. Minimum delivery for pen is 0.3 ml. ** For patients > 120 kg, use 80 µg/0.5 ml vial				

Duration of treatment
For patients who exhibit virological response at Week 12, treatment should be continued for at least another three-month period (i.e., a total of six months). The decision to extend therapy to one year of treatment should be based on prognostic factors (e.g., genotype, age > 40 years, male gender, bridging fibrosis).

Dose modification for all patients
If severe adverse reactions or laboratory abnormalities develop during treatment with PegIntron monotherapy or PegIntron in combination with ribavirin, modify the dosages of each product as appropriate, until the adverse reactions abate. Guidelines were developed in clinical trials for dose modification.

Combination Therapy Dose Reduction Guidelines

Table 2a Dose modification guidelines for combination therapy (with ribavirin)

Laboratory values	**Reduce only ribavirin dose to 600 mg/day* if:**	**Reduce only PegIntron dose to one-half dose if:**	**Discontinue combination therapy if:**
Haemoglobin	< 10 g/dl	-	< 8.5 g/dl
Haemoglobin in: Patients with history of stable cardiac disease	≥ 2 g/dl decrease in haemoglobin during any four week period during treatment (permanent dose reduction)		< 12 g/dl after four weeks of dose reduction
White blood cells	-	< 1.5 x 10^9/l	< 1.0 x 10^9/l
Neutrophils	-	< 0.75 x 10^9/l	< 0.5 x 10^9/l
Platelets	-	< 50 x 10^9/l	< 25 x 10^9/l
Bilirubin – direct	-	-	2.5 x ULN**
Bilirubin – indirect	> 5 mg/dl	-	> 4 mg/dl (for > 4 weeks)
Creatinine	-	-	> 2.0 mg/dl
ALT/AST	-	-	2 x baseline and > 10 x ULN**

* Patients whose dose of ribavirin is reduced to 600 mg daily receive one 200 mg capsule in the morning and two 200 mg capsules in the evening.

** Upper limit of normal

Dose reduction of PegIntron may be accomplished by either reducing the prescribed volume by one-half or by utilizing a lower dose strength as shown in **Table 2b**.

Table 2b – Reduced PegIntron Dosing for Combination Therapy

Body Weight (kg)	**Target Reduced Dose (µg)**	**Vial/Pen Strength (µg/0.5 ml)**	**Administer Once Weekly (ml)**	**Amount Delivered (µg)**
< 40	25	50*	0.25	25
40-50	32	50	0.3	30
51-64	40	50	0.4	40
65-75	50	50	0.5	50

76-85	60	80	0.4	64
> 85	75	100	0.4	80
*Must use vial. Minimum delivery for pen is 0.3 ml.				

PegIntron Monotherapy Dose Reduction Guidelines

Dose modification guidelines for patients who use PegIntron monotherapy are shown in **Table 3a.**

Table 3a Dose modification guidelines for PegIntron monotherapy		
Laboratory values	**Reduce PegIntron to one-half dose if:**	**Discontinue PegIntron if:**
Neutrophils	< 0.75 x 10^9/l	< 0.5 x 10^9/l
Platelets	< 50 x 10^9/l	< 25 x 10^9/l

Dose reduction for patients who use 0.5 µg/kg PegIntron monotherapy must be accomplished by reducing the prescribed volume by one-half. The 50 µg/0.5 ml vial must be used if necessary since the pen can only deliver a minimum volume of 0.3 ml.

For patients who use 1.0 µg/kg PegIntron monotherapy, dose reduction may be accomplished by reducing the prescribed volume by one-half or by utilizing a lower dose strength as shown in **Table 3b**.

Table 3b – Reduced PegIntron Dose for the 1.0 µg/kg Monotherapy Regimen				
Body Weight (kg)	**Target Reduced Dose (µg)**	**Vial/Pen Strength (µg/0.5ml)**	**Administer Once Weekly (ml)**	**Amount Delivered (µg)**
30-35	15	50*	0.15	15
36-45	20	50*	0.20	20
46-56	25	50*	0.25	25
57-72	32	50	0.3	30
73-89	40	50	0.4	40
90-106	50	50	0.5	50
> 106	60	80	0.4	64
*Must use vial. Minimum delivery for pen is 0.3 ml.				

Special populations

Use in renal impairment: The clearance of PegIntron is reduced in patients with significant renal impairment. Patients with creatinine clearance ≤ 50 ml/minute must not be treated with PegIntron (see section **5.2**). It is recommended that patients with moderate renal impairment be closely monitored and that their weekly dose of PegIntron be reduced if medically appropriate.

Use in hepatic impairment: The safety and efficacy of PegIntron therapy has not been evaluated in patients with severe hepatic dysfunction, therefore PegIntron must not be used for these patients.

Use in the elderly (≥ 65 years of age): There are no apparent age-related effects on the pharmacokinetics of PegIntron. Data from elderly patients treated with a single dose of PegIntron suggest no alteration in PegIntron dose is necessary based on age (see section **5.2**).

Use in patients under the age of 18 years: PegIntron is not recommended for use in children or adolescents under the age of 18, as there is no experience in this group.

4.3 Contraindications

- Hypersensitivity to the active substance or to any interferon or to any of the excipients;
- Pregnant women;
- Women who are breast-feeding;
- A history of severe pre-existing cardiac disease, including unstable or uncontrolled cardiac disease in the previous six months (see section **4.4**);
- Severe, debilitating medical conditions, including patients with chronic renal failure or creatinine clearance < 50 ml/minute;
- Autoimmune hepatitis or a history of autoimmune disease;
- Severe hepatic dysfunction or decompensated cirrhosis of the liver;
- Pre-existing thyroid disease unless it can be controlled with conventional treatment;
- Epilepsy and/or compromised central nervous system (CNS) function.

4.4 Special warnings and special precautions for use

There is no experience with PegIntron in combination with ribavirin in patients who have relapsed after interferon alpha + ribavirin therapy.

All patients in the chronic hepatitis C studies had a liver biopsy before inclusion, but in certain cases (i.e. patients with genotype 2 and 3), treatment may be possible without histological confirmation. Current treatment guidelines should be consulted as to whether a liver biopsy is needed prior to commencing treatment.

Acute hypersensitivity: Acute hypersensitivity reactions (e.g., urticaria, angioedema, bronchoconstriction, anaphylaxis) have been observed rarely during interferon alfa-2b therapy. If such a reaction develops during treatment with PegIntron, discontinue treatment and institute appropriate medical therapy immediately. Transient rashes do not necessitate interruption of treatment.

Cardiovascular system: As with interferon alfa-2b, patients with a history of congestive heart failure, myocardial infarction and/or previous or current arrhythmic disorders, receiving PegIntron therapy require close monitoring. It is recommended that patients who have pre-existing cardiac abnormalities have electrocardiograms taken prior to and during the course of treatment. Cardiac arrhythmias (primarily supraventricular) usually respond to conventional therapy but may require discontinuation of PegIntron therapy.

Psychiatric and Central Nervous System (CNS): If treatment with peginterferon alfa-2b is judged necessary in patients with existence or history of severe psychiatric conditions, this should only be initiated after having ensured appropriate individualised diagnostic and therapeutic management of the psychiatric condition.
Severe CNS effects, particularly depression, suicidal ideation and attempted suicide have been observed in some patients during PegIntron therapy. Other CNS effects including aggressive behaviour, confusion and alterations of mental status have been observed with alpha interferon. If patients develop psychiatric or CNS problems, including clinical depression, it is recommended that the patient be carefully monitored due to the potential seriousness of these undesirable effects. If symptoms persist or worsen, discontinue PegIntron therapy.
More significant obtundation and coma, including cases of encephalopathy, have been observed in some patients, usually elderly, treated at higher doses for oncology indications. While these effects are generally reversible, in a few patients full resolution took up to three weeks. Very rarely, seizures have occurred with high doses of interferon alpha.

Liver function: As with all interferons, discontinue treatment with PegIntron in patients who develop prolongation of coagulation markers which might indicate liver decompensation.

Fever: While fever may be associated with the flu-like syndrome reported commonly during interferon therapy, other causes of persistent fever must be ruled out.

Hydration: Adequate hydration must be maintained in patients undergoing PegIntron therapy since hypotension related to fluid depletion has been seen in some patients treated with alpha interferons. Fluid replacement may be necessary.

Pulmonary changes: Pulmonary infiltrates, pneumonitis, and pneumonia, occasionally resulting in fatality, have been observed rarely in interferon alpha treated patients. Any patient developing fever, cough, dyspnea or other respiratory symptoms must have a chest X-ray taken. If the chest X-ray shows pulmonary infiltrates or there is evidence of pulmonary function impairment, the patient is to be monitored closely, and, if appropriate, discontinue interferon alpha. Prompt discontinuation of interferon alpha administration and treatment with corticosteroids appear to be associated with resolution of pulmonary adverse events.

Autoimmune disease: The development of auto-antibodies and autoimmune disorders has been reported during treatment with alpha interferons. Patients predisposed to the development of autoimmune disorders may be at increased risk. Patients with signs or symptoms compatible with autoimmune disorders should be evaluated carefully, and the benefit-risk of continued interferon therapy should be reassessed (see also section **4.4 Thyroid changes** and **4.8**).

Ocular changes: Ophthalmologic disorders, including retinal haemorrhages, cotton wool spots, and retinal artery or vein obstruction have been reported in rare instances after treatment with alpha interferons (see section **4.8**). All patients should have a baseline eye examination. Any patient complaining of ocular symptoms, including loss of visual acuity or visual field must have a prompt and complete eye examination. Periodic visual examinations are recommended during PegIntron therapy, particularly in patients with disorders that may be associated with retinopathy, such as diabetes mellitus or hypertension. Discontinuation of PegIntron should be considered in patients who develop new or worsening ophthalmological disorders.

Thyroid changes: Infrequently, patients treated for chronic hepatitis C with interferon alpha have developed thyroid abnormalities, either hypothyroidism or hyperthyroidism. Determine thyroid stimulating hormone (TSH) levels if, during the course of therapy, a patient develops symptoms consistent with possible thyroid dysfunction. In the presence of thyroid dysfunction, PegIntron treatment may be continued if TSH levels can be maintained in the normal range by medication.

Metabolic disturbances: Hypertriglyceridemia and aggravation of hypertriglyceridemia, sometimes severe, have been observed. Monitoring of lipid levels is, therefore, recommended.

HCV/HIV Coinfection
Patients co-infected with HIV and receiving Highly Active Anti-Retroviral Therapy (HAART) may be at increased risk of developing lactic acidosis. Caution should be used when adding PegIntron and ribavirin to HAART therapy (see ribavirin SPC).
Co-infected patients with advanced cirrhosis receiving HAART may be at increased risk of hepatic decompensation and death. Adding treatment with alfa interferons alone or in combination with ribavirin may increase the risk in this patient subset.

Organ transplant recipients: The safety and efficacy of PegIntron alone or in combination with ribavirin for the treatment of hepatitis C in liver or other organ transplant recipients have not been studied. Preliminary data indicates that interferon alpha therapy may be associated with an increased rate of kidney graft rejection. Liver graft rejection has also been reported.

Other: Due to reports of interferon alpha exacerbating pre-existing psoriatic disease and sarcoidosis, use

of PegIntron in patients with psoriasis or sarcoidosis is recommended only if the potential benefit justifies the potential risk.

Laboratory tests: Standard haematologic tests, blood chemistry and a test of thyroid function must be conducted in all patients prior to initiating therapy. Acceptable baseline values that may be considered as a guideline prior to initiation of PegIntron therapy are:

- Platelets ≥ 100,000/mm^3
- Neutrophil count ≥ 1,500/mm^3
- TSH level must be within normal limits

Laboratory evaluations are to be conducted at weeks 2 and 4 of therapy, and periodically thereafter as clinically appropriate.

4.5 Interaction with other medicinal products and other forms of interaction

Results of a single-dose study with PegIntron demonstrated no effect on the activity of cytochrome (CY) P1A2, CYP2C8/9, CYP2D6, and hepatic CYP3A4 or N-acetyl transferase. Caution should be advised in the interpretation of these results as the use of other forms of interferon alpha result in a 50 % reduction in the clearance and thus a doubling of plasma concentrations of theophylline, a substrate of CYP1A2.

No pharmacokinetic interactions were noted between PegIntron and ribavirin in a multiple-dose pharmacokinetic study.

4.6 Pregnancy and lactation

There are no adequate data on the use of interferon alfa-2b in pregnant women. Interferon alfa-2b has been shown to be abortifacient in primates. PegIntron is likely to also cause this effect. PegIntron should not be used during pregnancy (see section **5.3**).

PegIntron is recommended for use in fertile women only when they are using effective contraception during the treatment period.

Lactation: It is not known whether the components of this medicinal product are excreted in human milk. Because of the potential for adverse reactions in nursing infants, nursing must be discontinued prior to initiation of treatment.

Ribavirin is teratogenic and embryocidal and must not be used in pregnant women (see ribavirin SPC, **5.3**).

4.7 Effects on ability to drive and use machines

Patients who develop fatigue, somnolence or confusion during treatment with PegIntron are cautioned to avoid driving or operating machinery.

4.8 Undesirable effects

The safety of PegIntron is evaluated from data from two clinical trials: one with PegIntron monotherapy, one with PegIntron in combination with ribavirin. In both cases, patients were treated for one year.

Table 4 describes the regimens and patient exposure for one year of treatment in patients with no previous exposure to interferon (interferon-naïve patients). Because of a significant overlap in the pattern of undesirable effects with PegIntron monotherapy, groups of patients have been brought together in **Table 5** to show the pattern of reported effects for all monotherapy groups.

Table 4	Regimens and patient exposure	
Treatment	**Regimen**	**Number of patients treated for one year**
PegIntron + ribavirin	PegIntron (1.5 micrograms/kg/week) + ribavirin (> 10.6 mg/kg/day)	188
Interferon alfa-2b + ribavirin	Interferon alfa-2b (3 MIU three times a week) + ribavirin (1,000/1,200 mg/day)	505
PegIntron monotherapy	PegIntron (0.5 microgram/kg/week)	315
	PegIntron (1.0 microgram/kg/week)	297
	PegIntron (1.5 micrograms/kg/week)	304

Table 5 Undesirable effects reported in clinical trials (≥ 10 % of patients in PegIntron + ribavirin group)			
	PegIntron + ribavirin	**Interferon alfa-2b + ribavirin**	**PegIntron monotherapy**
Application site disorder			
Injection site inflammation	20 %	17 %	39-44 %
Injection site reaction	54 %	36 %	7-9 %
Body as a whole			
Headache	58 %	57 %	57-63 %
Fatigue	56 %	59 %	43 %
Rigors	42 %	40 %	33-43 %
Fever	39 %	32 %	29-43 %
Flu-like symptoms	21 %	23 %	18-25 %
Asthenia	28 %	17 %	12-14 %
Weight decrease	30 %	19 %	8-18 %
Gastrointestinal			
Nausea	43 %	31 %	20-23 %
Anorexia	35 %	26 %	10-25 %
Diarrhoea	20 %	13 %	14-17 %
Abdominal pain	12 %	9 %	11 %
Vomiting	16 %	10 %	4-7 %
Musculoskeletal			
Myalgia	49 %	49 %	46-60 %
Arthralgia	31 %	26 %	23-28 %
Musculoskeletal pain	15 %	11 %	11-13 %
Psychiatric			
Depression	34 %	32 %	26 %
Irritability	32 %	34 %	19 %
Insomnia	37 %	41 %	16-19 %
Anxiety	14 %	14 %	8 %
Concentration impaired	18 %	21 %	9-10 %
Emotional lability	11 %	10 %	5 %
Respiratory system			
Pharyngitis	10 %	7 %	3 %
Coughing	14 %	11 %	4 %
Dyspnea	26 %	22 %	5 %
Skin and appendages			
Alopecia	45 %	32 %	20-34 %
Pruritus	27 %	27 %	7-9 %
Skin dry	23 %	21 %	6-9 %
Rash	21 %	21 %	5-7 %
Other			
Dizziness	17 %	16 %	7-12 %
Infection viral	10 %	5 %	4-5 %
Mouth dry	10 %	8 %	4-8 %

Table 6. Undesirable effects reported in clinical trials (1%-< 10% of patients treated with PegIntron + ribavirin or PegIntron monotherapy)		
Body system	**5-10%**	**1-<5%**
Body as a whole	chest pain, RUQ pain, malaise	erythema, injection site pain, flushing, thirst, herpes simplex, face or peripheral oedema, dehydration
Cardiovascular		tachycardia, palpitation, hypotension, hypertension, syncope
Central/peripheral nervous system	paresthesia	hypoaesthesia, hyperaesthesia, hypertonia, decreased libido, confusion, tremor, vertigo, migraine, tinnitus, hearing impairment/loss, ataxia, neuralgia
Endocrine	hypothyroidism,	hyperthyroidism, amenorrhoea, prostatitis, hyperuricemia, hypocalcemia
Gastrointestinal	dyspepsia,	constipation, taste perversion, loose stools, stomatitis, ulcerative stomatitis, gingival bleeding, glossitis, flatulence, hemorrhoids, gastroesophageal reflux, hepatomegaly, bilirubinemia, gingivitis
Haematologic	anaemia, leukopaenia	thrombocytopenia, lymphadenopathy,
Musculoskeletal		arthritis
Ocular		blurred vision, conjunctivitis, lacrimal gland disorder, eye pain
Psychiatric	agitation, nervousness	aggressive behaviour, somnolence, behavior disorder, apathy, appetite increased, sleep disorder, dreaming abnormal
Reproductive	menstrual disorder, menorrhagia	ovarian disorder, vaginal disorder, sexual dysfunction (not specified), impotence, breast pain
Respiratory		nonproductive cough, rhinitis, sinusitis, bronchitis, respiratory disorder, nasal congestion, rhinorrhea, dysphonia, epistaxis
Resistance mechanism		otitis media, fungal infection, bacterial infection
Skin and appendages	increased sweating	erythematous rash, eczema, photosensitivity reaction, maculopapular rash, abnormal hair texture, acne, dermatitis, furunculosis, nail disorder, psoriasis, urticaria
Urinary		micturition frequency, urine abnormal

Most cases of neutropaenia and thrombocytopaenia were mild (WHO grades 1 or 2). There were some cases of more severe neutropaenia in patients treated with the recommended doses of PegIntron in combination with ribavirin (WHO grade 3: 39 of 186 [21 %]; and WHO grade 4: 13 of 186 [7 %]).

In a clinical trial, approximately 1.2 % of patients treated with PegIntron or interferon alfa-2b in combination with ribavirin reported life-threatening psychiatric events during treatment. These events included suicidal ideation and attempted suicide (see section **4.4**). Following marketing, psychosis and hallucinations have been reported rarely.

Rarely reported events with interferon alfa-2b, including PegIntron, include seizure, pancreatitis, arrhythmia, peripheral neuropathy, diabetes, rhabdomyolysis, myositis, renal insufficiency and renal failure.

Cardiovascular (CVS) adverse events, particularly arrhythmia, appeared to be correlated mostly with pre-existing CVS disease and prior therapy with cardiotoxic agents (see section **4.4**). Cardiomyopathy, that may be reversible upon discontinuation of interferon alpha, has been reported rarely in patients without prior evidence of cardiac disease.

Very rarely cases of erythema multiforme, Stevens Johnson syndrome, toxic epidermal necrolysis, cardiac ischaemia, myocardial infarction, cerebrovascular ischaemia, cerebrovascular hemorrhage, encephalopathy, sarcoidosis or exacerbation of sarcoidosis, interstitial lung disease and injection site necrosis have been reported. Ulcerative and ischaemic colitis have been reported very rarely with PegIntron.

Very rarely, interferon alfa-2b or PegIntron used alone or in combination with ribavirin may be associated with aplastic anaemia.

Ophthalmological disorders that have been reported rarely with alpha interferons include retinopathies (including macular oedema), retinal haemorrhages, retinal artery or vein obstruction, cotton wool spots, loss of visual acuity or visual field, optic neuritis, and papilloedema (see section **4.4**).

A wide variety of autoimmune and immune-mediated disorders have been reported with alpha interferons including thyroid disorders, idiopathic and thrombotic thrombocytopenic purpura, vasculitis, neuropathies including mononeuropathies (see also section **4.4**, **Autoimmune disorders**).

4.9 Overdose

In clinical trials, cases of accidental overdose, at never more than twice the prescribed dose, were reported. There were no serious reactions. Undesirable effects resolved during continued administration of PegIntron.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunostimulants, Cytokines and immunomodulators, Interferons, Peginterferon alfa-2b, ATC code: L03A B10.

Recombinant interferon alfa-2b is covalently conjugated with monomethoxy polyethylene glycol at an average degree of substitution of 1 mole of polymer/mole of protein. The average molecular mass is approximately 31,300 daltons of which the protein moiety constitutes approximately 19,300.

Interferon alfa-2b
In vitro and *in vivo* studies suggest that the biological activity of PegIntron is derived from its interferon alfa-2b moiety.

Interferons exert their cellular activities by binding to specific membrane receptors on the cell surface. Studies with other interferons have demonstrated species specificity. However, certain monkey species, e.g., Rhesus monkeys, are susceptible to pharmacodynamic stimulation upon exposure to human type 1 interferons.

Once bound to the cell membrane, interferon initiates a complex sequence of intracellular events that include the induction of certain enzymes. It is thought that this process, at least in part, is responsible for the various cellular responses to interferon, including inhibition of virus replication in virus-infected cells, suppression of cell proliferation and such immunomodulating activities as enhancement

of the phagocytic activity of macrophages and augmentation of the specific cytotoxicity of lymphocytes for target cells. Any or all of these activities may contribute to interferon's therapeutic effects.

Recombinant interferon alfa-2b also inhibits viral replication *in vitro* and *in vivo*. Although the exact antiviral mode of action of recombinant interferon alfa-2b is unknown, it appears to alter the host cell metabolism. This action inhibits viral replication or if replication occurs, the progeny virions are unable to leave the cell.

PegIntron
PegIntron pharmacodynamics were assessed in a rising single-dose trial in healthy subjects by examining changes in oral temperature, concentrations of effector proteins such as serum neopterin and 2'5'-oligoadenylate synthetase (2'5'-OAS), as well as white cell and neutrophil counts. Subjects treated with PegIntron showed mild dose-related elevations in body temperature. Following single doses of PegIntron between 0.25 and 2.0 micrograms/kg/week, serum neopterin concentration was increased in a dose-related manner. Neutrophil and white cell count reductions at the end of week 4 correlated with the dose of PegIntron.

PegIntron clinical trials
Two pivotal trials have been conducted, one (C/I97-010) with PegIntron monotherapy; the other (C/I98-580) with PegIntron in combination with ribavirin. Eligible patients for these trials had chronic hepatitis C confirmed by a positive HCV-RNA polymerase chain reaction (PCR) assay (> 30 IU/ml), a liver biopsy consistent with a histological diagnosis of chronic hepatitis with no other cause for the chronic hepatitis, and abnormal serum ALT.

In the PegIntron monotherapy trial, a total of 916 naïve chronic hepatitis C patients were treated with PegIntron (0.5, 1.0 or 1.5 micrograms/kg/week) for one year with a follow-up period of six months. In addition, 303 patients received interferon alfa-2b (3 million International Units [MIU] three times a week as a comparator. This study showed that PegIntron was superior to interferon alfa-2b (**Table 7**).

In the PegIntron combination trial, 1,530 naïve patients were treated for one year with one of the following combination regimens:
- PegIntron (1.5 micrograms/kg/week) + ribavirin (800 mg/day), (n = 511).
- PegIntron (1.5 micrograms/kg/week for one month followed by 0.5 microgram/kg/week for 11 months) + ribavirin (1,000/1,200 mg/day), (n = 514).
- Interferon alfa-2b (3 MIU three times a week) + ribavirin (1,000/1,200 mg/day) (n = 505).

In this trial, the combination of PegIntron (1.5 micrograms/kg/week) and ribavirin was significantly more effective than the combination of interferon alfa-2b and ribavirin (**Table 7**), particularly in patients infected with Genotype 1 (**Table 8**). Sustained response was assessed by the response rate six months after the cessation of treatment.

HCV genotype and baseline virus load are prognostic factors which are known to affect response rates. However, response rates in this trial were shown to be dependent also on the dose of ribavirin administered in combination with PegIntron or interferon alfa-2b. In those patients that received > 10.6 mg/kg ribavirin (800 mg dose in typical 75 kg patient), regardless of genotype or viral load, response rates were significantly higher than in those patients that received ≤ 10.6 mg/kg ribavirin (**Table 8**), while response rates in patients that received > 13.2 mg/kg ribavirin were even higher.

Table 7 Sustained virological response (% patients HCV negative)

	PegIntron monotherapy				**PegIntron + ribavirin**		
Treatment regimen	**P 1.5**	**P 1.0**	**P 0.5**	**I**	**P 1.5/R**	**P 0.5/R**	**I/R**
Number of patients	304	297	315	303	511	514	505
Response at end of treatment	49 %	41 %	33 %	24 %	65 %	56 %	54 %

Sustained response	**23 %***	**25 %**	**18 %**	**12 %**	**54 %****	**47 %**	**47 %**

P 1.5 PegIntron 1.5 micrograms/kg
P 1.0 PegIntron 1.0 microgram/kg
P 0.5 PegIntron 0.5 microgram/kg
I Interferon alfa-2b 3 MIU
P 1.5/R PegIntron (1.5 micrograms/kg) + ribavirin (800 mg)
P 0.5/R PegIntron (1.5 to 0.5 microgram/kg) + ribavirin (1,000/1,200 mg)
I/R Interferon alfa-2b (3 MIU) + ribavirin (1,000/1,200 mg)
* $p < 0.001$ P 1.5 vs. I
** $p = 0.0143$ P 1.5/R vs. I/R

Table 8 Sustained response rates with PegIntron + ribavirin (by ribavirin dose, genotype and viral load)

HCV Genotype	Rebetol dose (mg/kg)	P 1.5/R	P 0.5/R	I/R
All Genotypes	**All**	**54 %**	**47 %**	**47 %**
	≤ 10.6	50 %	41 %	27 %
	> 10.6	61 %	48 %	47 %
Genotype 1	**All**	**42 %**	**34 %**	**33 %**
	≤ 10.6	38 %	25 %	20 %
	> 10.6	48 %	34 %	34 %
Genotype 1 ≤ 600,000 IU/ml	All	73 %	51 %	45 %
	≤ 10.6	74 %	25 %	33 %
	> 10.6	71 %	52 %	45 %
Genotype 1 > 600,000 IU/ml	All	30 %	27 %	29 %
	≤ 10.6	27 %	25 %	17 %
	> 10.6	37 %	27 %	29 %
Genotype 2/3	**All**	**82 %**	**80 %**	**79 %**
	≤ 10.6	79 %	73 %	50 %
	> 10.6	88 %	80 %	80 %

P 1.5/R PegIntron (1.5 micrograms/kg) + ribavirin (800 mg)
P 0.5/R PegIntron (1.5 to 0.5 microgram/kg) + ribavirin (1,000/1,200 mg)
I/R Interferon alfa-2b (3 MIU) + ribavirin (1,000/1,200 mg)

In the PegIntron monotherapy study, the Quality of Life was generally less affected by 0.5 microgram/kg of PegIntron than by either 1.0 microgram/kg of PegIntron once weekly or 3 MIU of interferon alfa-2b three times a week.

In a separate trial, 224 patients with genotype 2 or 3 received PegIntron, 1.5 microgram/kg subcutaneously, once weekly, in combination with ribavirin 800 mg –1,400 mg p.o. for 6 months (based on body weight, only three patients weighing > 105 kg, received the 1,400 mg dose, which has not yet been validated) (**Table 9**). Twenty-four % had bridging fibrosis or cirrhosis (Knodell 3/4).

Table 9. Virologic Response at End of Treatment, Sustained Virologic Response and Relapse by HCV Genotype and Viral Load*

	PegIntron 1.5 µg/kg Once Weekly Plus Rebetol 800-1400 mg/day		
	End of Treatment Response	Sustained Virologic Response	Relapse
All Subjects	94 % (211/224)	81 % (182/224)	12 % (27/224)
HCV 2	100 % (42/42)	93 % (39/42)	7 % (3/42)
≤ 600,000 IU/ml	100 % (20/20)	95 % (19/20)	5 % (1/20)
> 600,000 IU/mL	100 % (22/22)	91 % (20/22)	9 % (2/22)
HCV 3	93 % (169/182)	79 % (143/182)	14 %

			(24/166)
≤ 600,000 IU/ml	93 % (92/99)	86 % (85/99)	8 % (7/91)
> 600,000 IU/ml	93 % (77/83)	70 % (58/83)	23 % (17/75)

* Any subject with an undetectable HCV-RNA level at the Follow-Up Week 12 visit and missing data at the Follow-Up Week 24 visit was considered a sustained responder. Any subject with missing data in and after the Follow-Up Week 12 window was considered to be a non-responder at Week 24 of follow-up.

The 6 month treatment duration in this trial was better tolerated than one year of treatment in the pivotal combination trial; for discontinuation 5 % vs. 14 %, for dose modification 18 % vs. 49 %.

Predictability of sustained virological response
Virological reponse by week 12, defined as a 2-log viral load decrease or undetectable levels of HCV RNA has been shown to be predictive for sustained response (**Table 10**).

Table 10 Predictability of sustained response by viral response at week 12 and genotype*

Treatment	Genotype	Viral response at week 12	Sustained response	Negative predictive value
PegIntron 1.5 + ribavirin (> 10.6 mg/kg) 48-week treatment	1	Yes 75 % (82/110)	71 % (58/82)	----
		No 25 % (28/110)	0 % (0/28)	100 %
PegIntron 1.5 + ribavirin 800-1,400 mg 24-week treatment	2 and 3	Yes 99 % (213/215)	83 % (177/213)	----
		No 1 % (2/215)	50 % (1/2)	50 %

* reflects patients with 12 week data available

The negative predictive value for sustained response in patients treated with PegIntron in monotherapy was 98 %.

5.2 Pharmacokinetic properties

PegIntron is a well characterized polyethylene glycol-modified ("pegylated") derivative of interferon alfa-2b and is predominantly composed of monopegylated species. The plasma half-life of PegIntron is prolonged compared with non-pegylated interferon alfa-2b. PegIntron has a potential to depegylate to free interferon alfa-2b. The biologic activity of the pegylated isomers is qualitatively similar, but weaker than free interferon alfa-2b.

Following subcutaneous administration, maximal serum concentrations occur between 15-44 hours post-dose, and are sustained for up to 48-72 hours post-dose.

PegIntron C_{max} and AUC measurements increase in a dose-related manner. Mean apparent volume of distribution is 0.99 l/kg.

Upon multiple dosing, there is an accumulation of immunoreactive interferons. There is, however, only a modest increase in biologic activity as measured by a bioassay.

Mean (SD) PegIntron elimination half-life is approximately 40 hours (13.3 hours), with apparent clearance of 22.0 ml/hr·kg. The mechanisms involved in clearance of interferons in man have not yet been

fully elucidated. However, renal elimination may account for a minority (approximately 30 %) of PegIntron apparent clearance.

Renal function: Renal clearance appears to account for 30 % of total clearance of PegIntron. In a single dose study (1.0 microgram/kg) in patients with impaired renal function, C_{max}, AUC, and half-life increased in relation to the degree of renal impairment.

Based on these data, no dose modification is recommended based on creatinine clearance. However, because of marked intra-subject variability in interferon pharmacokinetics, it is recommended that patients be monitored closely during treatment with PegIntron (see section **4.2**). Patients with severe renal dysfunction or creatinine clearance < 50 ml/min must not be treated with PegIntron.

Hepatic function: The pharmacokinetics of PegIntron have not been evaluated in patients with severe hepatic dysfunction.

Elderly patients ≥ 65 years of age: The pharmacokinetics of PegIntron following a single subcutaneous dose of 1.0 microgram/kg were not affected by age. The data suggest that no alteration in PegIntron dosage is necessary based on advancing age.

Patients under the age of 18 years: Specific pharmacokinetic evaluations have not been performed on these patients. PegIntron is indicated for the treatment of chronic hepatitis C only in patients 18 years of age or older.

Interferon neutralising factors: Interferon neutralising factor assays were performed on serum samples of patients who received PegIntron in the clinical trial. Interferon neutralising factors are antibodies which neutralise the antiviral activity of interferon. The clinical incidence of neutralising factors in patients who received PegIntron 0.5 micrograms/kg is 1.1 %.

5.3 Preclinical safety data

PegIntron: Adverse events not observed in clinical trials were not seen in toxicity studies in monkeys. These studies were limited to four weeks due to the appearance of anti-interferon antibodies in most monkeys.

Reproduction studies of PegIntron have not been performed. Interferon alfa-2b has been shown to be an abortifacient in primates. PegIntron is likely to also cause this effect. Effects on fertility have not been determined. PegIntron showed no genotoxic potential. (see section **4.6** for relevant human data. It is not known whether the components of this medicinal product are excreted in human milk. Therefore, nursing must be discontinued prior to the initiation of therapy.)

The relative non-toxicity of monomethoxy-polyethylene glycol (mPEG), which is liberated from PegIntron by metabolism *in vivo* has been demonstrated in preclinical acute and subchronic toxicity studies in rodents and monkeys, standard embryo-foetal development studies and in *in vitro* mutagenicity assays.

PegIntron plus ribavirin: When used in combination with ribavirin, PegIntron did not cause any effects not previously seen with either active substance alone. The major treatment-related change was a reversible, mild to moderate anaemia, the severity of which was greater than that produced by either active substance alone.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder for solution for injection:

Disodium phosphate, anhydrous,

Sodium dihydrogen phosphate dihydrate,
Sucrose,
Polysorbate 80.
Solvent for parenteral use:
Water for injections.

Deliverable volume from pen = 0.5 ml. An overfill is also included for proper dispensing from the pen delivery system.

6.2 Incompatibilities

This medicinal product should only be reconstituted with the solvent provided and must not be mixed with other medicinal products (see also section **6.6**).

6.3 Shelf life

3 years

After reconstitution:
- Chemical and physical in-use stability has been demonstrated for 24 hours at 2°C - 8ºC.
- From a microbiological point of view, the product is to be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C - 8°C.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C). Do not freeze.

6.5 Nature and contents of container

The powder and solvent are both contained in a two-chamber cartridge, Type I flint glass, separated by a bromobutyl rubber plunger. The cartridge is sealed at one end with a polypropylene cap containing a bromobutyl rubber liner and at the other end by a bromobutyl rubber plunger.

PegIntron 120 micrograms is supplied as:
- 1 pen containing powder and solvent for solution for injection, 1 injection needle and 2 cleansing swabs;
- 4 pens containing powder and solvent for solution for injection, 4 injection needles and 8 cleansing swabs;
- 6 pens containing powder and solvent for solution for injection, 6 injection needles and 12 cleansing swabs;
- 12 pens containing powder and solvent for solution for injection, 12 injection needles and 24 cleansing swabs.

Not all pack sizes may be marketed.

6.6 Instructions for use and handling and disposal

PegIntron pre-filled pen contains a powder of peginterferon alfa-2b and a solvent for solution at a strength of 120 micrograms for single use. Each pen is reconstituted with the solvent provided in the two-chamber cartridge (water for injections) for administration of up to 0.5 ml of solution. A small volume is lost during preparation of PegIntron for injection when the dose is measured and injected. Therefore, each pen contains an excess amount of solvent and PegIntron powder to ensure delivery of the labelled dose in 0.5 ml of PegIntron, solution for injection. The reconstituted solution has a concentration of 120 micrograms in 0.5 ml.

PegIntron is injected subcutaneously after reconstituting the powder as instructed, attaching an injection

needle and setting the prescribed dose. A complete and illustrated set of instructions is provided in the Annex to the Package Leaflet.

Remove PegIntron pre-filled pen from the refrigerator before administration to allow the solvent to reach room temperature (not more than 25°C).

As for all parenteral medicinal products, inspect visually the reconstituted solution prior to administration. The reconstituted solution should be clear and colourless. Do not use if discolouration or particulate matter is present. After administering the dose, discard the PegIntron pre- filled pen and any unused solution contained in it.

7. MARKETING AUTHORISATION HOLDER

SP Europe
73, rue de Stalle
B-1180 Bruxelles
Belgium

8. MARKETING AUTHORISATION NUMBERS

EU/1/00/131/043
EU/1/00/131/044
EU/1/00/131/045
EU/1/00/131/046

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

6 February 2002

10. DATE OF REVISION OF THE TEXT

1. NAME OF THE MEDICINAL PRODUCT

PegIntron 150 micrograms, powder and solvent for solution for injection in pre-filled pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled pen of PegIntron 150 micrograms contains a sufficient amount of peginterferon alfa-2b as measured on a protein basis in a powder for solution for injection, and the corresponding amount of solvent, to provide 150 micrograms in 0.5 ml of peginterferon alfa-2b when reconstituted as recommended.

The active substance is a covalent conjugate of recombinant interferon alfa-2b* with monomethoxy polyethylene glycol. The potency of this product should not be compared to that of another pegylated or non-pegylated protein of the same therapeutic class. For more information, see section **5.1.**
*produced by rDNA technology in *E.coli* cells harbouring a genetically engineered plasmid hybrid encompassing an interferon alfa-2b gene from human leukocytes

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection
The white powder and the clear and colourless solvent are both contained in a two-chamber glass cartidge assembled into a single use pre-filled pen.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PegIntron is indicated for the treatment of adult patients with chronic hepatitis C who have elevated transaminases without liver decompensation and who are positive for serum HCV-RNA or anti-HCV (see section **4.4**).

The best way to use PegIntron in this indication is in combination with ribavirin.

This combination is indicated in naïve patients as well as in patients who have previously responded (with normalisation of ALT at the end of treatment) to interferon alpha monotherapy but who have subsequently relapsed.

Interferon monotherapy, including PegIntron, is indicated mainly in case of intolerance or contraindication to ribavirin.

Please refer also to the ribavirin Summary of Product Characteristics (SPC) when PegIntron is to be used in combination with ribavirin.

4.2 Posology and method of administration

Treatment should be initiated and monitored only by a physician experienced in the management of patients with hepatitis C.

Dose to be administered
PegIntron should be administered as a once weekly subcutaneous injection. The dose administered depends on whether it is used in combination with ribavirin or as monotherapy.

Combination therapy
PegIntron 1.5 micrograms/kg/week in combination with ribavirin capsules.

The intended dose of 1.5 μg/kg of PegIntron to be used in combination with ribavirin may be delivered in weight categories with the pen/vial strengths according to **Table 1**. Ribavirin capsules are to be administered orally each day in two divided doses with food (morning and evening).

Table 1 - Dosing for Combination Therapy

Body Weight (kg)	PegIntron		Ribavirin Capsules	
	Vial/Pen Strength (μg/0.5ml)	Administer Once Weekly (ml)	Total Daily Dose (mg)	Number of Capsules (200 mg)
< 40	50	0.5	800	4[a]
40-50	80	0.4	800	4[a]
51-64	80	0.5	800	4[a]
65-75	100	0.5	1,000	5[b]
76-85	120	0.5	1,000	5[b]
> 85	150	0.5	1,200	6[c]

a: 2 morning, 2 evening
b: 2 morning, 3 evening
c: 3 morning, 3 evening

Duration of treatment
Predictability of sustained virological response: Patients infected with virus genotype 1 who fail to achieve virological response at Week 12 are highly unlikely to become sustained virological responders (see also section **5.1**).

- **Genotype 1**: For patients who exhibit virological response at week 12, treatment should be continued for another nine month period (i.e., a total of 48 weeks).
- **Genotypes 2 or 3**: It is recommended that all patients be treated for 24 weeks.
- **Genotype 4:** In general, patients infected with genotype 4 are considered harder to treat and limited study data (n=66) indicate they are compatible with a posology as for genotype 1.

PegIntron monotherapy
As monotherapy the PegIntron regimen is 0.5 or 1.0 microgram/kg/week. The lowest vial or pen strength available is 50 μg/0.5 ml; therefore for patients prescribed 0.5 μg/kg/week, doses must be adjusted by volume as shown in **Table 2**. For the 1.0 μg/kg dose, similar volume adjustments can be made or alternate vial strengths can be used as shown in **Table 2**.

Table 2- Monotherapy Dosing

	0.5 μg/kg		1.0 μg/kg	
Body Weight (kg)	Vial/Pen Strength (μg/0.5ml)	Administer Once Weekly (ml)	Vial/Pen Strength (μg/0.5ml)	Administer Once Weekly (ml)
30-35	50*	0.15	50	0.3
36-45	50*	0.2	50	0.4
46-56	50*	0.25	50	0.5
57-72	50	0.3	80	0.4
73-88	50	0.4	80	0.5

89-106	50	0.5	100	0.5
> 106**	80	0.4	120	0.5
* Must use vial. Minimum delivery for pen is 0.3 ml. ** For patients > 120 kg, use 80 µg/0.5 ml vial				

Duration of treatment
For patients who exhibit virological response at Week 12, treatment should be continued for at least another three-month period (i.e., a total of six months). The decision to extend therapy to one year of treatment should be based on prognostic factors (e.g., genotype, age > 40 years, male gender, bridging fibrosis).

Dose modification for all patients
If severe adverse reactions or laboratory abnormalities develop during treatment with PegIntron monotherapy or PegIntron in combination with ribavirin, modify the dosages of each product as appropriate, until the adverse reactions abate. Guidelines were developed in clinical trials for dose modification.

Combination Therapy Dose Reduction Guidelines

Table 2a Dose modification guidelines for combination therapy (with ribavirin)

Laboratory values	**Reduce only ribavirin dose to 600 mg/day* if:**	**Reduce only PegIntron dose to one-half dose if:**	**Discontinue combination therapy if:**
Haemoglobin	< 10 g/dl	-	< 8.5 g/dl
Haemoglobin in: Patients with history of stable cardiac disease	≥ 2 g/dl decrease in haemoglobin during any four week period during treatment (permanent dose reduction)		< 12 g/dl after four weeks of dose reduction
White blood cells	-	< 1.5 x 10^9/l	< 1.0 x 10^9/l
Neutrophils	-	< 0.75 x 10^9/l	< 0.5 x 10^9/l
Platelets	-	< 50 x 10^9/l	< 25 x 10^9/l
Bilirubin – direct	-	-	2.5 x ULN**
Bilirubin – indirect	> 5 mg/dl	-	> 4 mg/dl (for > 4 weeks)
Creatinine	-	-	> 2.0 mg/dl
ALT/AST	-	-	2 x baseline and > 10 x ULN**

* Patients whose dose of ribavirin is reduced to 600 mg daily receive one 200 mg capsule in the morning and two 200 mg capsules in the evening.

** Upper limit of normal

Dose reduction of PegIntron may be accomplished by either reducing the prescribed volume by one-half or by utilizing a lower dose strength as shown in **Table 2b**.

Table 2b – Reduced PegIntron Dosing for Combination Therapy

Body Weight (kg)	**Target Reduced Dose (µg)**	**Vial/Pen Strength (µg/0.5 ml)**	**Administer Once Weekly (ml)**	**Amount Delivered (µg)**
< 40	25	50*	0.25	25
40-50	32	50	0.3	30
51-64	40	50	0.4	40
65-75	50	50	0.5	50

76-85	60	80	0.4	64
> 85	75	100	0.4	80
*Must use vial. Minimum delivery for pen is 0.3 ml.				

PegIntron Monotherapy Dose Reduction Guidelines

Dose modification guidelines for patients who use PegIntron monotherapy are shown in **Table 3a.**

Table 3a Dose modification guidelines for PegIntron monotherapy		
Laboratory values	**Reduce PegIntron to one-half dose if:**	**Discontinue PegIntron if:**
Neutrophils	< 0.75 x 10^9/l	< 0.5 x 10^9/l
Platelets	< 50 x 10^9/l	< 25 x 10^9/l

Dose reduction for patients who use 0.5 µg/kg PegIntron monotherapy must be accomplished by reducing the prescribed volume by one-half. The 50 µg/0.5 ml vial must be used if necessary since the pen can only deliver a minimum volume of 0.3 ml.

For patients who use 1.0 µg/kg PegIntron monotherapy, dose reduction may be accomplished by reducing the prescribed volume by one-half or by utilizing a lower dose strength as shown in **Table 3b**.

Table 3b – Reduced PegIntron Dose for the 1.0 µg/kg Monotherapy Regimen				
Body Weight (kg)	**Target Reduced Dose (µg)**	**Vial/Pen Strength (µg/0.5ml)**	**Administer Once Weekly (ml)**	**Amount Delivered (µg)**
30-35	15	50*	0.15	15
36-45	20	50*	0.20	20
46-56	25	50*	0.25	25
57-72	32	50	0.3	30
73-89	40	50	0.4	40
90-106	50	50	0.5	50
> 106	60	80	0.4	64
*Must use vial. Minimum delivery for pen is 0.3 ml.				

Special populations

Use in renal impairment: The clearance of PegIntron is reduced in patients with significant renal impairment. Patients with creatinine clearance ≤ 50 ml/minute must not be treated with PegIntron (see section **5.2**). It is recommended that patients with moderate renal impairment be closely monitored and that their weekly dose of PegIntron be reduced if medically appropriate.

Use in hepatic impairment: The safety and efficacy of PegIntron therapy has not been evaluated in patients with severe hepatic dysfunction, therefore PegIntron must not be used for these patients.

Use in the elderly (≥ 65 years of age): There are no apparent age-related effects on the pharmacokinetics of PegIntron. Data from elderly patients treated with a single dose of PegIntron suggest no alteration in PegIntron dose is necessary based on age (see section **5.2**).

Use in patients under the age of 18 years: PegIntron is not recommended for use in children or adolescents under the age of 18, as there is no experience in this group.

4.3 Contraindications

- Hypersensitivity to the active substance or to any interferon or to any of the excipients;
- Pregnant women;
- Women who are breast-feeding;
- A history of severe pre-existing cardiac disease, including unstable or uncontrolled cardiac disease in the previous six months (see section **4.4**);
- Severe, debilitating medical conditions, including patients with chronic renal failure or creatinine clearance < 50 ml/minute;
- Autoimmune hepatitis or a history of autoimmune disease;
- Severe hepatic dysfunction or decompensated cirrhosis of the liver;
- Pre-existing thyroid disease unless it can be controlled with conventional treatment;
- Epilepsy and/or compromised central nervous system (CNS) function.

4.4 Special warnings and special precautions for use

There is no experience with PegIntron in combination with ribavirin in patients who have relapsed after interferon alpha + ribavirin therapy.

All patients in the chronic hepatitis C studies had a liver biopsy before inclusion, but in certain cases (i.e. patients with genotype 2 and 3), treatment may be possible without histological confirmation. Current treatment guidelines should be consulted as to whether a liver biopsy is needed prior to commencing treatment.

Acute hypersensitivity: Acute hypersensitivity reactions (e.g., urticaria, angioedema, bronchoconstriction, anaphylaxis) have been observed rarely during interferon alfa-2b therapy. If such a reaction develops during treatment with PegIntron, discontinue treatment and institute appropriate medical therapy immediately. Transient rashes do not necessitate interruption of treatment.

Cardiovascular system: As with interferon alfa-2b, patients with a history of congestive heart failure, myocardial infarction and/or previous or current arrhythmic disorders, receiving PegIntron therapy require close monitoring. It is recommended that patients who have pre-existing cardiac abnormalities have electrocardiograms taken prior to and during the course of treatment. Cardiac arrhythmias (primarily supraventricular) usually respond to conventional therapy but may require discontinuation of PegIntron therapy.

Psychiatric and Central Nervous System (CNS): If treatment with peginterferon alfa-2b is judged necessary in patients with existence or history of severe psychiatric conditions, this should only be initiated after having ensured appropriate individualised diagnostic and therapeutic management of the psychiatric condition.
Severe CNS effects, particularly depression, suicidal ideation and attempted suicide have been observed in some patients during PegIntron therapy. Other CNS effects including aggressive behaviour, confusion and alterations of mental status have been observed with alpha interferon. If patients develop psychiatric or CNS problems, including clinical depression, it is recommended that the patient be carefully monitored due to the potential seriousness of these undesirable effects. If symptoms persist or worsen, discontinue PegIntron therapy.
More significant obtundation and coma, including cases of encephalopathy, have been observed in some patients, usually elderly, treated at higher doses for oncology indications. While these effects are generally reversible, in a few patients full resolution took up to three weeks. Very rarely, seizures have occurred with high doses of interferon alpha.

Liver function: As with all interferons, discontinue treatment with PegIntron in patients who develop prolongation of coagulation markers which might indicate liver decompensation.

Fever: While fever may be associated with the flu-like syndrome reported commonly during interferon therapy, other causes of persistent fever must be ruled out.

Hydration: Adequate hydration must be maintained in patients undergoing PegIntron therapy since hypotension related to fluid depletion has been seen in some patients treated with alpha interferons. Fluid replacement may be necessary.

Pulmonary changes: Pulmonary infiltrates, pneumonitis, and pneumonia, occasionally resulting in fatality, have been observed rarely in interferon alpha treated patients. Any patient developing fever, cough, dyspnea or other respiratory symptoms must have a chest X-ray taken. If the chest X-ray shows pulmonary infiltrates or there is evidence of pulmonary function impairment, the patient is to be monitored closely, and, if appropriate, discontinue interferon alpha. Prompt discontinuation of interferon alpha administration and treatment with corticosteroids appear to be associated with resolution of pulmonary adverse events.

Autoimmune disease: The development of auto-antibodies and autoimmune disorders has been reported during treatment with alpha interferons. Patients predisposed to the development of autoimmune disorders may be at increased risk. Patients with signs or symptoms compatible with autoimmune disorders should be evaluated carefully, and the benefit-risk of continued interferon therapy should be reassessed (see also section **4.4 Thyroid changes** and **4.8**).

Ocular changes: Ophthalmologic disorders, including retinal haemorrhages, cotton wool spots, and retinal artery or vein obstruction have been reported in rare instances after treatment with alpha interferons (see section **4.8**). All patients should have a baseline eye examination. Any patient complaining of ocular symptoms, including loss of visual acuity or visual field must have a prompt and complete eye examination. Periodic visual examinations are recommended during PegIntron therapy, particularly in patients with disorders that may be associated with retinopathy, such as diabetes mellitus or hypertension. Discontinuation of PegIntron should be considered in patients who develop new or worsening ophthalmological disorders.

Thyroid changes: Infrequently, patients treated for chronic hepatitis C with interferon alpha have developed thyroid abnormalities, either hypothyroidism or hyperthyroidism. Determine thyroid stimulating hormone (TSH) levels if, during the course of therapy, a patient develops symptoms consistent with possible thyroid dysfunction. In the presence of thyroid dysfunction, PegIntron treatment may be continued if TSH levels can be maintained in the normal range by medication.

Metabolic disturbances: Hypertriglyceridemia and aggravation of hypertriglyceridemia, sometimes severe, have been observed. Monitoring of lipid levels is, therefore, recommended.

HCV/HIV Coinfection
Patients co-infected with HIV and receiving Highly Active Anti-Retroviral Therapy (HAART) may be at increased risk of developing lactic acidosis. Caution should be used when adding PegIntron and ribavirin to HAART therapy (see ribavirin SPC).
Co-infected patients with advanced cirrhosis receiving HAART may be at increased risk of hepatic decompensation and death. Adding treatment with alfa interferons alone or in combination with ribavirin may increase the risk in this patient subset.

Organ transplant recipients: The safety and efficacy of PegIntron alone or in combination with ribavirin for the treatment of hepatitis C in liver or other organ transplant recipients have not been studied. Preliminary data indicates that interferon alpha therapy may be associated with an increased rate of kidney graft rejection. Liver graft rejection has also been reported.

Other: Due to reports of interferon alpha exacerbating pre-existing psoriatic disease and sarcoidosis, use

of PegIntron in patients with psoriasis or sarcoidosis is recommended only if the potential benefit justifies the potential risk.

Laboratory tests: Standard haematologic tests, blood chemistry and a test of thyroid function must be conducted in all patients prior to initiating therapy. Acceptable baseline values that may be considered as a guideline prior to initiation of PegIntron therapy are:

- Platelets ≥ 100,000/mm^3
- Neutrophil count ≥ 1,500/mm^3
- TSH level must be within normal limits

Laboratory evaluations are to be conducted at weeks 2 and 4 of therapy, and periodically thereafter as clinically appropriate.

4.5 Interaction with other medicinal products and other forms of interaction

Results of a single-dose study with PegIntron demonstrated no effect on the activity of cytochrome (CY) P1A2, CYP2C8/9, CYP2D6, and hepatic CYP3A4 or N-acetyl transferase. Caution should be advised in the interpretation of these results as the use of other forms of interferon alpha result in a 50 % reduction in the clearance and thus a doubling of plasma concentrations of theophylline, a substrate of CYP1A2.

No pharmacokinetic interactions were noted between PegIntron and ribavirin in a multiple-dose pharmacokinetic study.

4.6 Pregnancy and lactation

There are no adequate data on the use of interferon alfa-2b in pregnant women. Interferon alfa-2b has been shown to be abortifacient in primates. PegIntron is likely to also cause this effect. PegIntron should not be used during pregnancy (see section **5.3**).

PegIntron is recommended for use in fertile women only when they are using effective contraception during the treatment period.

Lactation: It is not known whether the components of this medicinal product are excreted in human milk. Because of the potential for adverse reactions in nursing infants, nursing must be discontinued prior to initiation of treatment.

Ribavirin is teratogenic and embryocidal and must not be used in pregnant women (see ribavirin SPC, **5.3**).

4.7 Effects on ability to drive and use machines

Patients who develop fatigue, somnolence or confusion during treatment with PegIntron are cautioned to avoid driving or operating machinery.

4.8 Undesirable effects

The safety of PegIntron is evaluated from data from two clinical trials: one with PegIntron monotherapy, one with PegIntron in combination with ribavirin. In both cases, patients were treated for one year.

Table 4 describes the regimens and patient exposure for one year of treatment in patients with no previous exposure to interferon (interferon-naïve patients). Because of a significant overlap in the pattern of undesirable effects with PegIntron monotherapy, groups of patients have been brought together in **Table 5** to show the pattern of reported effects for all monotherapy groups.

Table 4	Regimens and patient exposure	
Treatment	**Regimen**	**Number of patients treated for one year**
PegIntron + ribavirin	PegIntron (1.5 micrograms/kg/week) + ribavirin (> 10.6 mg/kg/day)	188
Interferon alfa-2b + ribavirin	Interferon alfa-2b (3 MIU three times a week) + ribavirin (1,000/1,200 mg/day)	505
PegIntron monotherapy	PegIntron (0.5 microgram/kg/week)	315
	PegIntron (1.0 microgram/kg/week)	297
	PegIntron (1.5 micrograms/kg/week)	304

Table 5 Undesirable effects reported in clinical trials (≥ 10 % of patients in PegIntron + ribavirin group)			
	PegIntron + ribavirin	**Interferon alfa-2b + ribavirin**	**PegIntron monotherapy**
Application site disorder			
Injection site inflammation	20 %	17 %	39-44 %
Injection site reaction	54 %	36 %	7-9 %
Body as a whole			
Headache	58 %	57 %	57-63 %
Fatigue	56 %	59 %	43 %
Rigors	42 %	40 %	33-43 %
Fever	39 %	32 %	29-43 %
Flu-like symptoms	21 %	23 %	18-25 %
Asthenia	28 %	17 %	12-14 %
Weight decrease	30 %	19 %	8-18 %
Gastrointestinal			
Nausea	43 %	31 %	20-23 %
Anorexia	35 %	26 %	10-25 %
Diarrhoea	20 %	13 %	14-17 %
Abdominal pain	12 %	9 %	11 %
Vomiting	16 %	10 %	4-7 %
Musculoskeletal			
Myalgia	49 %	49 %	46-60 %
Arthralgia	31 %	26 %	23-28 %
Musculoskeletal pain	15 %	11 %	11-13 %
Psychiatric			
Depression	34 %	32 %	26 %
Irritability	32 %	34 %	19 %
Insomnia	37 %	41 %	16-19 %
Anxiety	14 %	14 %	8 %
Concentration impaired	18 %	21 %	9-10 %
Emotional lability	11 %	10 %	5 %
Respiratory system			
Pharyngitis	10 %	7 %	3 %
Coughing	14 %	11 %	4 %
Dyspnea	26 %	22 %	5 %
Skin and appendages			
Alopecia	45 %	32 %	20-34 %
Pruritus	27 %	27 %	7-9 %
Skin dry	23 %	21 %	6-9 %
Rash	21 %	21 %	5-7 %
Other			
Dizziness	17 %	16 %	7-12 %
Infection viral	10 %	5 %	4-5 %
Mouth dry	10 %	8 %	4-8 %

Table 6. Undesirable effects reported in clinical trials (1%-< 10% of patients treated with PegIntron + ribavirin or PegIntron monotherapy)		
Body system	**5-10%**	**1-<5%**
Body as a whole	chest pain, RUQ pain, malaise	erythema, injection site pain, flushing, thirst, herpes simplex, face or peripheral oedema, dehydration
Cardiovascular		tachycardia, palpitation, hypotension, hypertension, syncope
Central/peripheral nervous system	paresthesia	hypoaesthesia, hyperaesthesia, hypertonia, decreased libido, confusion, tremor, vertigo, migraine, tinnitus, hearing impairment/loss, ataxia, neuralgia
Endocrine	hypothyroidism,	hyperthyroidism, amenorrhoea, prostatitis, hyperuricemia, hypocalcemia
Gastrointestinal	dyspepsia,	constipation, taste perversion, loose stools, stomatitis, ulcerative stomatitis, gingival bleeding, glossitis, flatulence, hemorrhoids, gastroesophageal reflux, hepatomegaly, bilirubinemia, gingivitis
Haematologic	anaemia, leukopaenia	thrombocytopenia, lymphadenopathy,
Musculoskeletal		arthritis
Ocular		blurred vision, conjunctivitis, lacrimal gland disorder, eye pain
Psychiatric	agitation, nervousness	aggressive behaviour, somnolence, behavior disorder, apathy, appetite increased, sleep disorder, dreaming abnormal
Reproductive	menstrual disorder, menorrhagia	ovarian disorder, vaginal disorder, sexual dysfunction (not specified), impotence, breast pain
Respiratory		nonproductive cough, rhinitis, sinusitis, bronchitis, respiratory disorder, nasal congestion, rhinorrhea, dysphonia, epistaxis
Resistance mechanism		otitis media, fungal infection, bacterial infection
Skin and appendages	increased sweating	erythematous rash, eczema, photosensitivity reaction, maculopapular rash, abnormal hair texture, acne, dermatitis, furunculosis, nail disorder, psoriasis, urticaria
Urinary		micturition frequency, urine abnormal

Most cases of neutropaenia and thrombocytopaenia were mild (WHO grades 1 or 2). There were some cases of more severe neutropaenia in patients treated with the recommended doses of PegIntron in combination with ribavirin (WHO grade 3: 39 of 186 [21 %]; and WHO grade 4: 13 of 186 [7 %]).

In a clinical trial, approximately 1.2 % of patients treated with PegIntron or interferon alfa-2b in combination with ribavirin reported life-threatening psychiatric events during treatment. These events included suicidal ideation and attempted suicide (see section **4.4**). Following marketing, psychosis and hallucinations have been reported rarely.

Rarely reported events with interferon alfa-2b, including PegIntron, include seizure, pancreatitis, arrhythmia, peripheral neuropathy, diabetes, rhabdomyolysis, myositis, renal insufficiency and renal failure.

Cardiovascular (CVS) adverse events, particularly arrhythmia, appeared to be correlated mostly with pre-existing CVS disease and prior therapy with cardiotoxic agents (see section **4.4**). Cardiomyopathy, that may be reversible upon discontinuation of interferon alpha, has been reported rarely in patients without prior evidence of cardiac disease.

Very rarely cases of erythema multiforme, Stevens Johnson syndrome, toxic epidermal necrolysis, cardiac ischaemia, myocardial infarction, cerebrovascular ischaemia, cerebrovascular hemorrhage, encephalopathy, sarcoidosis or exacerbation of sarcoidosis, interstitial lung disease and injection site necrosis have been reported. Ulcerative and ischaemic colitis have been reported very rarely with PegIntron.

Very rarely, interferon alfa-2b or PegIntron used alone or in combination with ribavirin may be associated with aplastic anaemia.

Ophthalmological disorders that have been reported rarely with alpha interferons include retinopathies (including macular oedema), retinal haemorrhages, retinal artery or vein obstruction, cotton wool spots, loss of visual acuity or visual field, optic neuritis, and papilloedema (see section **4.4**).

A wide variety of autoimmune and immune-mediated disorders have been reported with alpha interferons including thyroid disorders, idiopathic and thrombotic thrombocytopenic purpura, vasculitis, neuropathies including mononeuropathies (see also section **4.4**, **Autoimmune disorders**).

4.9 Overdose

In clinical trials, cases of accidental overdose, at never more than twice the prescribed dose, were reported. There were no serious reactions. Undesirable effects resolved during continued administration of PegIntron.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunostimulants, Cytokines and immunomodulators, Interferons, Peginterferon alfa-2b, ATC code: L03A B10.

Recombinant interferon alfa-2b is covalently conjugated with monomethoxy polyethylene glycol at an average degree of substitution of 1 mole of polymer/mole of protein. The average molecular mass is approximately 31,300 daltons of which the protein moiety constitutes approximately 19,300.

Interferon alfa-2b
In vitro and *in vivo* studies suggest that the biological activity of PegIntron is derived from its interferon alfa-2b moiety.

Interferons exert their cellular activities by binding to specific membrane receptors on the cell surface. Studies with other interferons have demonstrated species specificity. However, certain monkey species, e.g., Rhesus monkeys, are susceptible to pharmacodynamic stimulation upon exposure to human type 1 interferons.

Once bound to the cell membrane, interferon initiates a complex sequence of intracellular events that include the induction of certain enzymes. It is thought that this process, at least in part, is responsible for the various cellular responses to interferon, including inhibition of virus replication in virus-infected cells, suppression of cell proliferation and such immunomodulating activities as enhancement

of the phagocytic activity of macrophages and augmentation of the specific cytotoxicity of lymphocytes for target cells. Any or all of these activities may contribute to interferon's therapeutic effects.

Recombinant interferon alfa-2b also inhibits viral replication *in vitro* and *in vivo*. Although the exact antiviral mode of action of recombinant interferon alfa-2b is unknown, it appears to alter the host cell metabolism. This action inhibits viral replication or if replication occurs, the progeny virions are unable to leave the cell.

PegIntron
PegIntron pharmacodynamics were assessed in a rising single-dose trial in healthy subjects by examining changes in oral temperature, concentrations of effector proteins such as serum neopterin and 2'5'-oligoadenylate synthetase (2'5'-OAS), as well as white cell and neutrophil counts. Subjects treated with PegIntron showed mild dose-related elevations in body temperature. Following single doses of PegIntron between 0.25 and 2.0 micrograms/kg/week, serum neopterin concentration was increased in a dose-related manner. Neutrophil and white cell count reductions at the end of week 4 correlated with the dose of PegIntron.

PegIntron clinical trials
Two pivotal trials have been conducted, one (C/I97-010) with PegIntron monotherapy; the other (C/I98-580) with PegIntron in combination with ribavirin. Eligible patients for these trials had chronic hepatitis C confirmed by a positive HCV-RNA polymerase chain reaction (PCR) assay (> 30 IU/ml), a liver biopsy consistent with a histological diagnosis of chronic hepatitis with no other cause for the chronic hepatitis, and abnormal serum ALT.

In the PegIntron monotherapy trial, a total of 916 naïve chronic hepatitis C patients were treated with PegIntron (0.5, 1.0 or 1.5 micrograms/kg/week) for one year with a follow-up period of six months. In addition, 303 patients received interferon alfa-2b (3 million International Units [MIU] three times a week as a comparator. This study showed that PegIntron was superior to interferon alfa-2b (**Table 7**).

In the PegIntron combination trial, 1,530 naïve patients were treated for one year with one of the following combination regimens:
- PegIntron (1.5 micrograms/kg/week) + ribavirin (800 mg/day), (n = 511).
- PegIntron (1.5 micrograms/kg/week for one month followed by 0.5 microgram/kg/week for 11 months) + ribavirin (1,000/1,200 mg/day), (n = 514).
- Interferon alfa-2b (3 MIU three times a week) + ribavirin (1,000/1,200 mg/day) (n = 505).

In this trial, the combination of PegIntron (1.5 micrograms/kg/week) and ribavirin was significantly more effective than the combination of interferon alfa-2b and ribavirin (**Table 7**), particularly in patients infected with Genotype 1 (**Table 8**). Sustained response was assessed by the response rate six months after the cessation of treatment.

HCV genotype and baseline virus load are prognostic factors which are known to affect response rates. However, response rates in this trial were shown to be dependent also on the dose of ribavirin administered in combination with PegIntron or interferon alfa-2b. In those patients that received > 10.6 mg/kg ribavirin (800 mg dose in typical 75 kg patient), regardless of genotype or viral load, response rates were significantly higher than in those patients that received ≤ 10.6 mg/kg ribavirin (**Table 8**), while response rates in patients that received > 13.2 mg/kg ribavirin were even higher.

Table 7 Sustained virological response (% patients HCV negative)

	PegIntron monotherapy				**PegIntron + ribavirin**		
Treatment regimen	**P 1.5**	**P 1.0**	**P 0.5**	**I**	**P 1.5/R**	**P 0.5/R**	**I/R**
Number of patients	304	297	315	303	511	514	505
Response at end of treatment	49 %	41 %	33 %	24 %	65 %	56 %	54 %

Sustained response	**23 %***	**25 %**	**18 %**	**12 %**	**54 %****	**47 %**	**47 %**

P 1.5 PegIntron 1.5 micrograms/kg
P 1.0 PegIntron 1.0 microgram/kg
P 0.5 PegIntron 0.5 microgram/kg
I Interferon alfa-2b 3 MIU
P 1.5/R PegIntron (1.5 micrograms/kg) + ribavirin (800 mg)
P 0.5/R PegIntron (1.5 to 0.5 microgram/kg) + ribavirin (1,000/1,200 mg)
I/R Interferon alfa-2b (3 MIU) + ribavirin (1,000/1,200 mg)
* $p < 0.001$ P 1.5 vs. I
** $p = 0.0143$ P 1.5/R vs. I/R

Table 8 Sustained response rates with PegIntron + ribavirin (by ribavirin dose, genotype and viral load)

HCV Genotype	Rebetol dose (mg/kg)	P 1.5/R	P 0.5/R	I/R
All Genotypes	**All**	**54 %**	**47 %**	**47 %**
	≤ 10.6	50 %	41 %	27 %
	> 10.6	61 %	48 %	47 %
Genotype 1	**All**	**42 %**	**34 %**	**33 %**
	≤ 10.6	38 %	25 %	20 %
	> 10.6	48 %	34 %	34 %
Genotype 1 ≤ 600,000 IU/ml	All	73 %	51 %	45 %
	≤ 10.6	74 %	25 %	33 %
	> 10.6	71 %	52 %	45 %
Genotype 1 > 600,000 IU/ml	All	30 %	27 %	29 %
	≤ 10.6	27 %	25 %	17 %
	> 10.6	37 %	27 %	29 %
Genotype 2/3	**All**	**82 %**	**80 %**	**79 %**
	≤ 10.6	79 %	73 %	50 %
	> 10.6	88 %	80 %	80 %

P 1.5/R PegIntron (1.5 micrograms/kg) + ribavirin (800 mg)
P 0.5/R PegIntron (1.5 to 0.5 microgram/kg) + ribavirin (1,000/1,200 mg)
I/R Interferon alfa-2b (3 MIU) + ribavirin (1,000/1,200 mg)

In the PegIntron monotherapy study, the Quality of Life was generally less affected by 0.5 microgram/kg of PegIntron than by either 1.0 microgram/kg of PegIntron once weekly or 3 MIU of interferon alfa-2b three times a week.

In a separate trial, 224 patients with genotype 2 or 3 received PegIntron, 1.5 microgram/kg subcutaneously, once weekly, in combination with ribavirin 800 mg –1,400 mg p.o. for 6 months (based on body weight, only three patients weighing > 105 kg, received the 1,400 mg dose, which has not yet been validated) (**Table 9**). Twenty-four % had bridging fibrosis or cirrhosis (Knodell 3/4).

Table 9. Virologic Response at End of Treatment, Sustained Virologic Response and Relapse by HCV Genotype and Viral Load*

	PegIntron 1.5 µg/kg Once Weekly Plus Rebetol 800-1400 mg/day		
	End of Treatment Response	Sustained Virologic Response	Relapse
All Subjects	94 % (211/224)	81 % (182/224)	12 % (27/224)
HCV 2	100 % (42/42)	93 % (39/42)	7 % (3/42)
≤ 600,000 IU/ml	100 % (20/20)	95 % (19/20)	5 % (1/20)
> 600,000 IU/mL	100 % (22/22)	91 % (20/22)	9 % (2/22)
HCV 3	93 % (169/182)	79 % (143/182)	14 %

			(24/166)
≤ 600,000 IU/ml	93 % (92/99)	86 % (85/99)	8 % (7/91)
> 600,000 IU/ml	93 % (77/83)	70 % (58/83)	23 % (17/75)

* Any subject with an undetectable HCV-RNA level at the Follow-Up Week 12 visit and missing data at the Follow-Up Week 24 visit was considered a sustained responder. Any subject with missing data in and after the Follow-Up Week 12 window was considered to be a non-responder at Week 24 of follow-up.

The 6 month treatment duration in this trial was better tolerated than one year of treatment in the pivotal combination trial; for discontinuation 5 % vs. 14 %, for dose modification 18 % vs. 49 %.

Predictability of sustained virological response
Virological reponse by week 12, defined as a 2-log viral load decrease or undetectable levels of HCV RNA has been shown to be predictive for sustained response (**Table 10**).

Table 10 Predictability of sustained response by viral response at week 12 and genotype*

Treatment	Genotype	Viral response at week 12	Sustained response	Negative predictive value
PegIntron 1.5 + ribavirin (> 10.6 mg/kg) 48-week treatment	1	Yes 75 % (82/110)	71 % (58/82)	----
		No 25 % (28/110)	0 % (0/28)	100 %
PegIntron 1.5 + ribavirin 800-1,400 mg 24-week treatment	2 and 3	Yes 99 % (213/215)	83 % (177/213)	----
		No 1 % (2/215)	50 % (1/2)	50 %

* reflects patients with 12 week data available

The negative predictive value for sustained response in patients treated with PegIntron in monotherapy was 98 %.

5.2 Pharmacokinetic properties

PegIntron is a well characterized polyethylene glycol-modified ("pegylated") derivative of interferon alfa-2b and is predominantly composed of monopegylated species. The plasma half-life of PegIntron is prolonged compared with non-pegylated interferon alfa-2b. PegIntron has a potential to depegylate to free interferon alfa-2b. The biologic activity of the pegylated isomers is qualitatively similar, but weaker than free interferon alfa-2b.

Following subcutaneous administration, maximal serum concentrations occur between 15-44 hours post-dose, and are sustained for up to 48-72 hours post-dose.

PegIntron C_{max} and AUC measurements increase in a dose-related manner. Mean apparent volume of distribution is 0.99 l/kg.

Upon multiple dosing, there is an accumulation of immunoreactive interferons. There is, however, only a modest increase in biologic activity as measured by a bioassay.

Mean (SD) PegIntron elimination half-life is approximately 40 hours (13.3 hours), with apparent clearance of 22.0 ml/hr·kg. The mechanisms involved in clearance of interferons in man have not yet been

fully elucidated. However, renal elimination may account for a minority (approximately 30 %) of PegIntron apparent clearance.

Renal function: Renal clearance appears to account for 30 % of total clearance of PegIntron. In a single dose study (1.0 microgram/kg) in patients with impaired renal function, C_{max}, AUC, and half-life increased in relation to the degree of renal impairment.

Based on these data, no dose modification is recommended based on creatinine clearance. However, because of marked intra-subject variability in interferon pharmacokinetics, it is recommended that patients be monitored closely during treatment with PegIntron (see section **4.2**). Patients with severe renal dysfunction or creatinine clearance < 50 ml/min must not be treated with PegIntron.

Hepatic function: The pharmacokinetics of PegIntron have not been evaluated in patients with severe hepatic dysfunction.

Elderly patients ≥ 65 years of age: The pharmacokinetics of PegIntron following a single subcutaneous dose of 1.0 microgram/kg were not affected by age. The data suggest that no alteration in PegIntron dosage is necessary based on advancing age.

Patients under the age of 18 years: Specific pharmacokinetic evaluations have not been performed on these patients. PegIntron is indicated for the treatment of chronic hepatitis C only in patients 18 years of age or older.

Interferon neutralising factors: Interferon neutralising factor assays were performed on serum samples of patients who received PegIntron in the clinical trial. Interferon neutralising factors are antibodies which neutralise the antiviral activity of interferon. The clinical incidence of neutralising factors in patients who received PegIntron 0.5 micrograms/kg is 1.1 %.

5.3 Preclinical safety data

PegIntron: Adverse events not observed in clinical trials were not seen in toxicity studies in monkeys. These studies were limited to four weeks due to the appearance of anti-interferon antibodies in most monkeys.

Reproduction studies of PegIntron have not been performed. Interferon alfa-2b has been shown to be an abortifacient in primates. PegIntron is likely to also cause this effect. Effects on fertility have not been determined. PegIntron showed no genotoxic potential. (see section **4.6** for relevant human data. It is not known whether the components of this medicinal product are excreted in human milk. Therefore, nursing must be discontinued prior to the initiation of therapy.)

The relative non-toxicity of monomethoxy-polyethylene glycol (mPEG), which is liberated from PegIntron by metabolism *in vivo* has been demonstrated in preclinical acute and subchronic toxicity studies in rodents and monkeys, standard embryo-foetal development studies and in *in vitro* mutagenicity assays.

PegIntron plus ribavirin: When used in combination with ribavirin, PegIntron did not cause any effects not previously seen with either active substance alone. The major treatment-related change was a reversible, mild to moderate anaemia, the severity of which was greater than that produced by either active substance alone.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder for solution for injection:

Disodium phosphate, anhydrous,

Sodium dihydrogen phosphate dihydrate,
Sucrose,
Polysorbate 80.
Solvent for parenteral use:
Water for injections.

Deliverable volume from pen = 0.5 ml. An overfill is also included for proper dispensing from the pen delivery system.

6.2 Incompatibilities

This medicinal product should only be reconstituted with the solvent provided and must not be mixed with other medicinal products (see also section **6.6**).

6.3 Shelf life

3 years

After reconstitution:
- Chemical and physical in-use stability has been demonstrated for 24 hours at 2°C - 8ºC.
- From a microbiological point of view, the product is to be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C - 8°C.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C). Do not freeze.

6.5 Nature and contents of container

The powder and solvent are both contained in a two-chamber cartridge, Type I flint glass, separated by a bromobutyl rubber plunger. The cartridge is sealed at one end with a polypropylene cap containing a bromobutyl rubber liner and at the other end by a bromobutyl rubber plunger.

PegIntron 150 micrograms is supplied as:
- 1 pen containing powder and solvent for solution for injection, 1 injection needle and 2 cleansing swabs;
- 4 pens containing powder and solvent for solution for injection, 4 injection needles and 8 cleansing swabs;
- 6 pens containing powder and solvent for solution for injection, 6 injection needles and 12 cleansing swabs;
- 12 pens containing powder and solvent for solution for injection, 12 injection needles and 24 cleansing swabs.

Not all pack sizes may be marketed.

6.6 Instructions for use and handling and disposal

PegIntron pre-filled pen contains a powder of peginterferon alfa-2b and a solvent for solution at a strength of 150 micrograms for single use. Each pen is reconstituted with the solvent provided in the two-chamber cartridge (water for injections) for administration of up to 0.5 ml of solution. A small volume is lost during preparation of PegIntron for injection when the dose is measured and injected. Therefore, each pen contains an excess amount of solvent and PegIntron powder to ensure delivery of the labelled dose in 0.5 ml of PegIntron, solution for injection. The reconstituted solution has a concentration of 150 micrograms in 0.5 ml.

PegIntron is injected subcutaneously after reconstituting the powder as instructed, attaching an injection

needle and setting the prescribed dose. A complete and illustrated set of instructions is provided in the Annex to the Package Leaflet.

Remove PegIntron pre-filled pen from the refrigerator before administration to allow the solvent to reach room temperature (not more than 25°C).

As for all parenteral medicinal products, inspect visually the reconstituted solution prior to administration. The reconstituted solution should be clear and colourless. Do not use if discolouration or particulate matter is present. After administering the dose, discard the PegIntron pre- filled pen and any unused solution contained in it.

7. MARKETING AUTHORISATION HOLDER

SP Europe
73, rue de Stalle
B-1180 Bruxelles
Belgium

8. MARKETING AUTHORISATION NUMBERS

EU/1/00/131/047
EU/1/00/131/048
EU/1/00/131/049
EU/1/00/131/050

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

6 February 2002

10. DATE OF REVISION OF THE TEXT

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

SP (Brinny) Company
Innishannon - County Cork
Ireland

Name and address of the manufacturer responsible for batch release

SP (Brinny) Company
Innishannon - County Cork
Ireland

B. CONDITIONS OF THE MARKETING AUTHORISATION

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, 4.2).

- **OTHER CONDITIONS**

The holder of this marketing authorisation must inform the European Commission about the marketing plans for the medicinal product authorised by this decision.

ANNEX III

LABELLING AND PACKAGE LEAFLET

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

PegIntron 50 micrograms

1. NAME OF THE MEDICINAL PRODUCT

PegIntron 50 micrograms powder and solvent for solution for injection
peginterferon alfa-2b

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial of powder contains 50 micrograms of peginterferon alfa-2b and
provides 50 micrograms/0.5 ml of peginterferon alfa-2b when reconstituted as recommended.
One ampoule of solvent contains 0.7 ml of water for injections.

3. LIST OF EXCIPIENTS

Excipients: disodium phosphate, anhydrous; sodium dihydrogen phosphate dihydrate, sucrose and polysorbate 80. Solvent: water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

1 vial of powder, 1 ampoule of solvent
1 vial of powder, 1 ampoule of solvent, 1 injection syringe, 2 injection needles and 1 cleansing swab
4 vials of powder, 4 ampoules of solvent
4 vials of powder, 4 ampoules of solvent, 4 injection syringes, 8 injection needles and 4 cleansing swabs
6 vials of powder, 6 ampoules of solvent
12 vials of powder, 12 ampoules of solvent, 12 injection syringes, 24 injection needles and 12 cleansing swabs
50 micrograms/0.5 ml

5. METHOD AND, IF NECESSARY, ROUTE(S) OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

After withdrawal of the dose, any remaining solution must be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing authorisation holder: SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

12. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

EU/1/00/131/001 (1 vial of powder, 1 ampoule of solvent)
EU/1/00/131/002 (1 vial of powder, 1 ampoule of solvent, 1 injection syringe, 2 injection needles and 1 cleansing swab)
EU/1/00/131/003 (4 vials of powder, 4 ampoules of solvent)
EU/1/00/131/004 (4 vials of powder, 4 ampoules of solvent, 4 injection syringes, 8 injection needles and 4 cleansing swabs)
EU/1/00/131/005 (6 vials of powder, 6 ampoules of solvent)
EU/1/00/131/026 (12 vials of powder, 12 ampoules of solvent, 12 injection syringes, 24 injection needles and 12 cleansing swabs)

13. MANUFACTURER'S BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PegIntron 50 micrograms – vial of powder

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

PegIntron 50 micrograms powder for injection
S.C.

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

50 micrograms/0.5 ml

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

PegIntron 80 micrograms

1. NAME OF THE MEDICINAL PRODUCT

PegIntron 80 micrograms powder and solvent for solution for injection
peginterferon alfa-2b

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial of powder contains 80 micrograms of peginterferon alfa-2b and
provides 80 micrograms/0.5 ml of peginterferon alfa-2b when reconstituted as recommended.
One ampoule of solvent contains 0.7 ml of water for injections.

3. LIST OF EXCIPIENTS

Excipients: disodium phosphate, anhydrous; sodium dihydrogen phosphate dihydrate, sucrose and polysorbate 80. Solvent: water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

1 vial of powder, 1 ampoule of solvent
1 vial of powder, 1 ampoule of solvent, 1 injection syringe, 2 injection needles and 1 cleansing swab
4 vials of powder, 4 ampoules of solvent
4 vials of powder, 4 ampoules of solvent, 4 injection syringes, 8 injection needles and 4 cleansing swabs
6 vials of powder, 6 ampoules of solvent
12 vials of powder, 12 ampoules of solvent, 12 injection syringes, 24 injection needles and 12 cleansing swabs
80 micrograms/0.5 ml

5. METHOD AND, IF NECESSARY, ROUTE(S) OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

After withdrawal of the dose, any remaining solution must be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing authorisation holder: SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

12. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

EU/1/00/131/006 (1 vial of powder, 1 ampoule of solvent)
EU/1/00/131/007 (1 vial of powder, 1 ampoule of solvent, 1 injection syringe, 2 injection needles and 1 cleansing swab)
EU/1/00/131/008 (4 vials of powder, 4 ampoules of solvent)
EU/1/00/131/009 (4 vials of powder, 4 ampoules of solvent, 4 injection syringes, 8 injection needles and 4 cleansing swabs)
EU/1/00/131/010 (6 vials of powder, 6 ampoules of solvent)
EU/1/00/131/027 (12 vials of powder, 12 ampoules of solvent, 12 injection syringes, 24 injection needles and 12 cleansing swabs)

13. MANUFACTURER'S BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PegIntron 80 micrograms - vial of powder

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

PegIntron 80 micrograms powder for injection
S.C.

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

80 micrograms/0.5 ml

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

PegIntron 100 micrograms

1. NAME OF THE MEDICINAL PRODUCT

PegIntron 100 micrograms powder and solvent for solution for injection
peginterferon alfa-2b

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial of powder contains 100 micrograms of peginterferon alfa-2b and
provides 100 micrograms/0.5 ml of peginterferon alfa-2b when reconstituted as recommended.
One ampoule of solvent contains 0.7 ml of water for injections.

3. LIST OF EXCIPIENTS

Excipients: disodium phosphate, anhydrous; sodium dihydrogen phosphate dihydrate, sucrose and polysorbate 80. Solvent: water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

1 vial of powder, 1 ampoule of solvent
1 vial of powder, 1 ampoule of solvent, 1 injection syringe, 2 injection needles and 1 cleansing swab
4 vials of powder, 4 ampoules of solvent
4 vials of powder, 4 ampoules of solvent, 4 injection syringes, 8 injection needles and 4 cleansing swabs
6 vials of powder, 6 ampoules of solvent
12 vials of powder, 12 ampoules of solvent, 12 injection syringes, 24 injection needles and 12 cleansing swabs
100 micrograms/0.5 ml

5. METHOD AND, IF NECESSARY, ROUTE(S) OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

After withdrawal of the dose, any remaining solution must be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing authorisation holder: SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

12. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

EU/1/00/131/011 (1 vial of powder, 1 ampoule of solvent)
EU/1/00/131/012 (1 vial of powder, 1 ampoule of solvent, 1 injection syringe, 2 injection needles and 1 cleansing swab)
EU/1/00/131/013 (4 vials of powder, 4 ampoules of solvent)
EU/1/00/131/014 (4 vials of powder, 4 ampoules of solvent, 4 injection syringes, 8 injection needles and 4 cleansing swabs)
EU/1/00/131/015 (6 vials of powder, 6 ampoules of solvent)
EU/1/00/131/028 (12 vials of powder, 12 ampoules of solvent, 12 injection syringes, 24 injection needles and 12 cleansing swabs)

13. MANUFACTURER'S BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PegIntron 100 micrograms - vial of powder

1. NAME OF THE MEDICINAL PRODUCT AND IF NECESSARY ROUTE(S) OF ADMINISTRATION

PegIntron 100 micrograms powder for injection
S.C.

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

100 micrograms/0.5 ml

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

PegIntron 120 micrograms

1. NAME OF THE MEDICINAL PRODUCT

PegIntron 120 micrograms powder and solvent for solution for injection
peginterferon alfa-2b

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial of powder contains 120 micrograms of peginterferon alfa-2b and
provides 120 micrograms/0.5 ml of peginterferon alfa-2b when reconstituted as recommended.
One ampoule of solvent contains 0.7 ml of water for injections.

3. LIST OF EXCIPIENTS

Excipients: disodium phosphate, anhydrous; sodium dihydrogen phosphate dihydrate, sucrose and polysorbate 80. Solvent: water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

1 vial of powder, 1 ampoule of solvent
1 vial of powder, 1 ampoule of solvent, 1 injection syringe, 2 injection needles and 1 cleansing swab
4 vials of powder, 4 ampoules of solvent
4 vials of powder, 4 ampoules of solvent, 4 injection syringes, 8 injection needles and 4 cleansing swabs
6 vials of powder, 6 ampoules of solvent
12 vials of powder, 12 ampoules of solvent, 12 injection syringes, 24 injection needles and 12 cleansing swabs
120 micrograms/0.5 ml

5. METHOD AND, IF NECESSARY, ROUTE(S) OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

After withdrawal of the dose, any remaining solution must be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing authorisation holder: SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

12. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

EU/1/00/131/016 (1 vial of powder, 1 ampoule of solvent)
EU/1/00/131/017 (1 vial of powder, 1 ampoule of solvent, 1 injection syringe, 2 injection needles and 1 cleansing swab)
EU/1/00/131/018 (4 vials of powder, 4 ampoules of solvent)
EU/1/00/131/019 (4 vials of powder, 4 ampoules of solvent, 4 injection syringes, 8 injection needles and 4 cleansing swabs)
EU/1/00/131/020 (6 vials of powder, 6 ampoules of solvent)
EU/1/00/131/029 (12 vials of powder, 12 ampoules of solvent, 12 injection syringes, 24 injection needles and 12 cleansing swabs)

13. MANUFACTURER'S BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PegIntron 120 micrograms - vial of powder

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

PegIntron 120 micrograms powder for injection
S.C.

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

120 micrograms/0.5 ml

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

PegIntron 150 micrograms

1. NAME OF THE MEDICINAL PRODUCT

PegIntron 150 micrograms powder and solvent for solution for injection
peginterferon alfa-2b

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial of powder contains 150 micrograms of peginterferon alfa-2b and
provides 150 micrograms/0.5 ml of peginterferon alfa-2b when reconstituted as recommended.
One ampoule of solvent contains 0.7 ml of water for injections.

3. LIST OF EXCIPIENTS

Excipients: disodium phosphate, anhydrous; sodium dihydrogen phosphate dihydrate, sucrose and polysorbate 80. Solvent: water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

1 vial of powder, 1 ampoule of solvent
1 vial of powder, 1 ampoule of solvent, 1 injection syringe, 2 injection needles and 1 cleansing swab
4 vials of powder, 4 ampoules of solvent
4 vials of powder, 4 ampoules of solvent, 4 injection syringes, 8 injection needles and 4 cleansing swabs
6 vials of powder, 6 ampoules of solvent
12 vials of powder, 12 ampoules of solvent, 12 injection syringes, 24 injection needles and 12 cleansing swabs
150 micrograms/0.5 ml

5. METHOD AND, IF NECESSARY, ROUTE(S) OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

After withdrawal of the dose, any remaining solution must be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing authorisation holder: SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

12. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

EU/1/00/131/021 (1 vial of powder, 1 ampoule of solvent)
EU/1/00/131/022 (1 vial of powder, 1 ampoule of solvent, 1 injection syringe, 2 injection needles and 1 cleansing swab)
EU/1/00/131/023 (4 vials of powder, 4 ampoules of solvent)
EU/1/00/131/024 (4 vials of powder, 4 ampoules of solvent, 4 injection syringes, 8 injection needles and 4 cleansing swabs)
EU/1/00/131/025 (6 vials of powder, 6 ampoules of solvent)
EU/1/00/131/030 (12 vials of powder, 12 ampoules of solvent, 12 injection syringes, 24 injection needles and 12 cleansing swabs)

13. MANUFACTURER'S BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PegIntron 150 micrograms - vial of powder

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

PegIntron 150 micrograms powder for injection
S.C.

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

150 micrograms/0.5 ml

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PegIntron - ampoule of solvent

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Solvent for PegIntron
Water for injections

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.7 ml

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

PegIntron 50 micrograms powder and solvent for solution for injection

1. NAME OF THE MEDICINAL PRODUCT

PegIntron 50 micrograms powder and solvent for solution for injection pre-filled pen
peginterferon alfa-2b

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One PegIntron pre-filled pen contains a sufficient amount of peginterferon alfa-2b to provide 50 micrograms in 0.5 ml of peginterferon alfa-2b when reconstituted as recommended.

3. LIST OF EXCIPIENTS

Excipients: disodium phosphate, anhydrous; sodium dihydrogen phosphate dihydrate, sucrose and polysorbate 80. Solvent: water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

1 pen, 1 injection needle and 2 cleansing swabs
4 pens, 4 injection needles and 8 cleansing swabs
6 pens, 6 injection needles and 12 cleansing swabs
12 pens, 12 injection needles and 24 cleansing swabs
50 micrograms/0.5 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

After injection of the dose, discard the pen in an appropriate container.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing authorisation holder: SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/00/131/031 (1 pen, 1 injection needle and 2 cleansing swabs)
EU/1/00/131/032 (4 pens, 4 injection needles and 8 cleansing swabs)
EU/1/00/131/033 (6 pens, 6 injection needles and 12 cleansing swabs)
EU/1/00/131/034 (12 pens, 12 injection needles and 24 cleansing swabs)

13. MANUFACTURER'S BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PegIntron 50 micrograms powder and solvent for solution for injection

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

PegIntron 50 micrograms powder and solvent for injection
S.C.

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

50 micrograms/0.5 ml

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

PegIntron 80 micrograms powder and solvent for solution for injection

1. NAME OF THE MEDICINAL PRODUCT

PegIntron 80 micrograms powder and solvent for solution for injection pre-filled pen
peginterferon alfa-2b

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One PegIntron pre-filled pen contains a sufficient amount of peginterferon alfa-2b to provide 80 micrograms in 0.5 ml of peginterferon alfa-2b when reconstituted as recommended.

3. LIST OF EXCIPIENTS

Excipients: disodium phosphate, anhydrous; sodium dihydrogen phosphate dihydrate, sucrose and polysorbate 80. Solvent: water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

1 pen, 1 injection needle and 2 cleansing swabs
4 pens, 4 injection needles and 8 cleansing swabs
6 pens, 6 injection needles and 12 cleansing swabs
12 pens, 12 injection needles and 24 cleansing swabs
80 micrograms/0.5 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

After injection of the dose, discard the pen in an appropriate container.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing authorisation holder: SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/00/131/035 (1 pen, 1 injection needle and 2 cleansing swabs)
EU/1/00/131/036 (4 pens, 4 injection needles and 8 cleansing swabs)
EU/1/00/131/037 (6 pens, 6 injection needles and 12 cleansing swabs)
EU/1/00/131/038 (12 pens, 12 injection needles and 24 cleansing swabs)

13. MANUFACTURER'S BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PegIntron 80 micrograms powder and solvent for solution for injection

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

PegIntron 80 micrograms powder and solvent for injection
S.C.

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

80 micrograms/0.5 ml

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

PegIntron 100 micrograms powder and solvent for solution for injection

1. NAME OF THE MEDICINAL PRODUCT

PegIntron 100 micrograms powder and solvent for solution for injection pre-filled pen
peginterferon alfa-2b

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One PegIntron pre-filled pen contains a sufficient amount of peginterferon alfa-2b to provide 100 micrograms in 0.5 ml of peginterferon alfa-2b when reconstituted as recommended.

3. LIST OF EXCIPIENTS

Excipients: disodium phosphate, anhydrous; sodium dihydrogen phosphate dihydrate, sucrose and polysorbate 80. Solvent: water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

1 pen, 1 injection needle and 2 cleansing swabs
4 pens, 4 injection needles and 8 cleansing swabs
6 pens, 6 injection needles and 12 cleansing swabs
12 pens, 12 injection needles and 24 cleansing swabs
100 micrograms/0.5 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

After injection of the dose, discard the pen in an appropriate container.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing authorisation holder: SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/00/131/039 (1 pen, 1 injection needle and 2 cleansing swabs)
EU/1/00/131/040 (4 pens, 4 injection needles and 8 cleansing swabs)
EU/1/00/131/041 (6 pens, 6 injection needles and 12 cleansing swabs)
EU/1/00/131/042 (12 pens, 12 injection needles and 24 cleansing swabs)

13. MANUFACTURER'S BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PegIntron 100 micrograms powder and solvent for solution for injection

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

PegIntron 100 micrograms powder and solvent for injection
S.C.

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

100 micrograms/0.5 ml

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

PegIntron 120 micrograms powder and solvent for solution for injection

1. NAME OF THE MEDICINAL PRODUCT

PegIntron 120 micrograms powder and solvent for solution for injection pre-filled pen
peginterferon alfa-2b

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One PegIntron pre-filled pen contains a sufficient amount of peginterferon alfa-2b to provide 120 micrograms in 0.5 ml of peginterferon alfa-2b when reconstituted as recommended.

3. LIST OF EXCIPIENTS

Excipients: disodium phosphate, anhydrous; sodium dihydrogen phosphate dihydrate, sucrose and polysorbate 80. Solvent: water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

1 pen, 1 injection needle and 2 cleansing swabs
4 pens, 4 injection needles and 8 cleansing swabs
6 pens, 6 injection needles and 12 cleansing swabs
12 pens, 12 injection needles and 24 cleansing swabs
120 micrograms/0.5 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

After injection of the dose, discard the pen in an appropriate container.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing authorisation holder: SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/00/131/043 (1 pen, 1 injection needle and 2 cleansing swabs)
EU/1/00/131/044 (4 pens, 4 injection needles and 8 cleansing swabs)
EU/1/00/131/045 (6 pens, 6 injection needles and 12 cleansing swabs)
EU/1/00/131/046 (12 pens, 12 injection needles and 24 cleansing swabs)

13. MANUFACTURER'S BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PegIntron 120 micrograms powder and solvent for solution for injection

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

PegIntron 120 micrograms powder and solvent for injection
S.C.

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

120 micrograms/0.5 ml

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

PegIntron 150 micrograms powder and solvent for solution for injection

1. NAME OF THE MEDICINAL PRODUCT

PegIntron 150 micrograms powder and solvent for solution for injection pre-filled pen
peginterferon alfa-2b

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One PegIntron pre-filled pen contains a sufficient amount of peginterferon alfa-2b to provide 150 micrograms in 0.5 ml of peginterferon alfa-2b when reconstituted as recommended.

3. LIST OF EXCIPIENTS

Excipients: disodium phosphate, anhydrous; sodium dihydrogen phosphate dihydrate, sucrose and polysorbate 80. Solvent: water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

1 pen, 1 injection needle and 2 cleansing swabs
4 pens, 4 injection needles and 8 cleansing swabs
6 pens, 6 injection needles and 12 cleansing swabs
12 pens, 12 injection needles and 24 cleansing swabs
150 micrograms/0.5 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

After injection of the dose, discard the pen in an appropriate container.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing authorisation holder: SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/00/131/047 (1 pen, 1 injection needle and 2 cleansing swabs)
EU/1/00/131/048 (4 pens, 4 injection needles and 8 cleansing swabs)
EU/1/00/131/049 (6 pens, 6 injection needles and 12 cleansing swabs)
EU/1/00/131/050 (12 pens, 12 injection needles and 24 cleansing swabs)

13. MANUFACTURER'S BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PegIntron 150 micrograms powder and solvent for solution for injection

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

PegIntron 150 micrograms powder and solvent for injection
S.C.

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

150 micrograms/0.5 ml

B. PACKAGE LEAFLET

PACKAGE LEAFLET

Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

In this leaflet:

PegIntron 50 micrograms powder and solvent for solution for injection
peginterferon alfa-2b (conjugation of recombinant interferon alfa-2b with monomethoxy polyethylene glycol)

- The active substance is peginterferon alfa-2b, 50 micrograms/0.5 ml.
- The other ingredients are:
  Powder: disodium phosphate, anhydrous; sodium dihydrogen phosphate dihydrate, sucrose and polysorbate 80;
  Solvent: water for injections 0.7 ml/ampoule.

Marketing Authorisation Holder: SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

Manufacturer: SP (Brinny) Company, Innishannon, County Cork, Ireland

1. WHAT PEGINTRON IS AND WHAT IT IS USED FOR

The pharmaceutical form is: powder and solvent for solution for injection.
The white powder is contained in a 2 ml glass vial and the clear and colourless solvent is presented in a 2 ml glass ampoule.

PegIntron 50 micrograms is available in different pack sizes:
- 1 vial of powder for solution for injection and 1 ampoule of solvent for parenteral use;
- 1 vial of powder for solution for injection, 1 ampoule of solvent for parenteral use, 1 injection syringe, 2 injection needles and 1 cleansing swab;
- 4 vials of powder for solution for injection and 4 ampoules of solvent for parenteral use;
- 4 vials of powder for solution for injection, 4 ampoules of solvent for parenteral use, 4 injection syringes, 8 injection needles and 4 cleansing swabs;
- 6 vials of powder for solution for injection and 6 ampoules of solvent for parenteral use;
- 12 vials of powder for solution for injection, 12 ampoules of solvent for parenteral use, 12 injection syringes, 24 injection needles and 12 cleansing swabs.

Not all pack sizes may be marketed.

Interferons modify the response of the body's immune system to help fight infections and severe diseases. PegIntron, which contains an interferon, is used for the treatment of chronic hepatitis C, a viral infection of the liver.

PegIntron is best used for this treatment in combination with ribavirin.

PegIntron is used alone in case of intolerance or contraindication to ribavirin.

2. BEFORE YOU USE PEGINTRON

PegIntron is not recommended for use in patients under the age of 18 years.

Do not use PegIntron:
- If you are hypersensitive (allergic) to peginterferon alfa-2b or any of the other ingredients of PegIntron.
- If you are hypersensitive (allergic) to any interferon.
- If you are pregnant or breast feeding.
- If you have had severe heart problems, or if you have heart disease that has not been well controlled during the past 6 months.
- If you have severe medical conditions that leave you very weak, including severe kidney disease.
- If you have autoimmune hepatitis or any other problem with your immune system; if you are taking medicine that suppresses your immune system (your immune system protects you against infection and some diseases).
- If you have advanced, uncontrolled liver disease (other than hepatitis C).
- If you have thyroid disease that is not well controlled with medicines.
- If you have a condition that causes convulsions (seizures, or "fits").

Take special care with PegIntron:
- If you develop symptoms of a severe allergic reaction (such as difficulty in breathing, wheezing, or hives) while on this medication, seek medical help immediately.
- If you ever had a heart attack or a heart problem.
- If you have ever been treated for depression or any other nervous or mental disorder.
- If you have had a problem with your liver (other than hepatitis C).
- If you develop symptoms associated with a cold or other respiratory infection, such as fever, cough, or any difficulty in breathing, tell your doctor.
- If you are diabetic, your doctor may ask you to have an eye examination.
- If you have had any serious illness affecting your breathing or your blood.
- If you have psoriasis, it may become worse while you are using PegIntron.
- If you are planning to become pregnant, discuss this with your doctor before starting to use PegIntron.
- If you are also being treated for HIV, please see **Using other medicines**.
- If you have had a severe nervous or mental disorder.
- If you have received an organ transplant, either kidney or liver, interferon treatment may increase the risk of rejection. Be sure to discuss this with your doctor.

While being treated with PegIntron
Your doctor may want you to drink extra fluids to help prevent low blood pressure.

Pregnancy
Ask your doctor or pharmacist for advice before taking any medicine. Do not use PegIntron during pregnancy. The effect on human pregnancy is not known.

Breast-feeding
Ask your doctor or pharmacist for advice before taking any medicine. It is not known whether this product is present in human milk. Therefore, do not breast-feed an infant if you are taking PegIntron.

Driving and using machines:
Do not drive or operate any tools or machines if you feel tired, sleepy or confused while taking PegIntron.

Using other medicines:

Please inform your doctor or pharmacist if you are taking or have recently taken any other medicines, even those not prescribed.

Important information about some of the ingredients of PegIntron:
This medicinal product contains less than 1 mmol sodium (23 mg) per 0.7 ml, i.e., essentially "sodium-free".

Patients who also have HIV infection:
Lactic acidosis and worsening liver function are side effects associated with Highly Active Anti-Retroviral Therapy (HAART), an HIV treatment. If you are receiving HAART, the addition of PegIntron and ribavirin may increase your risk of lactic acidosis and of liver failure. Your doctor will monitor you for signs and symptoms of these conditions. (Please be sure to read the ribavirin Patient Leaflet also).

3. HOW TO USE PEGINTRON

Your doctor has prescribed PegIntron specifically for you and your current condition; do not share this medicine with anyone else.

Your doctor has determined your dose of PegIntron based on your weight. If necessary, the dose may be changed during treatment.

Combination treatment
PegIntron, when given with ribavirin capsules, is usually given at a dose of 1.5 microgram/kg once a week.

Ribavirin capsules are taken every day, morning and evening. The number of ribavirin capsules you take depends on your weight.
- If you weigh less than 65 kg, take 2 capsules in the morning and 2 in the evening (total of 800 mg each day).
- If you weigh between 65 and 85 kg, take 2 capsules in the morning and 3 in the evening (total of 1,000 mg each day).
- If you weigh more than 85 kg, take 3 capsules in the morning and 3 in the evening (total 1,200 mg each day).

The combination treatment is continued for at least 6 months, and sometimes for one year.

PegIntron alone:
PegIntron, when given alone, is usually given at a dose of 0.5 or 1.0 microgram/kg once a week, for at least 6 months, and possibly for 1 year.

All patients:
If you are injecting PegIntron yourself, please be sure that the dose that has been prescribed for you is clearly provided on the package of medicine you receive.

If you have the impression that the effect of PegIntron is too strong or too weak, talk to your doctor or pharmacist.

PegIntron is intended for subcutaneous use. This means that it is injected through a short injection needle into the fatty tissue just under your skin. If you are injecting this medicine yourself, you will be instructed how to prepare and give the injection. Detailed instructions for subcutaneous administration are provided with this leaflet (see How to self-inject PegIntron at the end of the package leaflet).

Prepare the dose just before you intend to inject it and use it immediately. Look carefully at the reconstituted solution prior to administration. Do not use if there is discolouration of the reconstituted solution or if particulate matter is present. Discard any solution that is left in the vial after you give

yourself the injection.

Inject PegIntron once each week on the same day. Injecting it at the same time of day each week will help you not to forget to take it.

Use PegIntron exactly as prescribed by your doctor. Do not exceed the recommended dosage, and take it for as long as prescribed.

If you use more PegIntron than you should:
Tell your doctor or healthcare professional as soon as possible.

If you forget to take PegIntron:
Take the dose as soon as you remember, then continue your treatment as usual.
Do not take a double dose to make up for forgotten individual doses. Contact your doctor or pharmacist if needed.

4. POSSIBLE SIDE EFFECTS

Like all medicines, PegIntron can have side effects. Although not all of these side effects may occur, they may need medical attention if they do.

Check with your doctor immediately if any of the following side effects occur: chest pain; changes in the way your heart beats; breathing problems, (including shortness of breath), confusion; feeling depressed, wanting to harm yourself, hallucinations, numbness or tingling feeling; dizziness, convulsion ("fit"); trouble sleeping, thinking or concentrating; difficulty remaining alert, severe stomach pain or cramps; blood or clots in stool (or black, tarry stool); fever or chills beginning after a few weeks of treatment, pain in your lower back or side; difficulty or inability to pass urine, painful or inflamed muscles (sometimes severe); problems with your eyes or your eyesight or hearing; severe or painful reddening of your skin or mucous membrane, severe bleeding from your nose. Your doctor will test your blood to ensure that your white blood cell (cells that fight infection) and red blood cell (cells that carry oxygen) counts, platelets (blood clotting cells) and other laboratory values are at acceptable levels.

Some people get depressed when taking PegIntron alone or in combination treatment with ribavirin, and in some cases people had suicidal thoughts or aggressive behaviour. Some patients have actually committed suicide. Be sure to seek emergency care if you notice that you are becoming depressed or have suicidal thoughts or change in your behaviour. You may want to consider asking a family member or close friend to help you stay alert to signs of depression or changes in your behaviour.

The most common side effects with the combination of PegIntron and ribavirin capsules are irritation or redness (and rarely, skin damage) at the site of injection, headache, tired feeling, shaking chills, fever, flu-like symptoms, weakness, loss of weight, nausea, loss of appetite, diarrhoea or loose stools, stomach pain, vomiting, muscle aches, pain in joints and muscles, feeling depressed, irritability, trouble falling asleep or staying asleep, feeling anxious or nervous, difficulty concentrating, mood swings, hair loss, itching, dry skin, sore throat, coughing, difficult breathing, dizziness, virus infection, rash, and dry mouth.

Other common side effects that may occur with combination treatment are increased sweating, chest pain, pain on the right side around your ribs, numbness, pain or tingling feeling, change in thyroid gland activity (which may make you feel tired or, less commonly, energetic), stomach upset, rapid heart rate, agitation, nervousness, difficult or irregular menstrual period.

Less common are pain at the place of injection, flushing, low or high blood pressure, dry or teary eyes, redness of skin or skin disorders, psoriasis, hives, nail disorder, feeling unwell, feeling faint, poor coordination, confusion, increased or decreased sensitivity to touch, tense muscles, arthritis, bruising, loss of interest in activities including sex, sexual problem, unusual dreams, shaky hands, vertigo (spinning feeling), increased appetite, heartburn, intestinal gas (flatus), constipation, hemorrhoids, red or bleeding

gums, redness or sores in mouth, change in taste, changes in hearing or ringing in ears, thirst, aggressive or changed behaviour, feeling sleepy, cold sores, fungal or bacterial infections, irritation of prostate gland, increased need to pass urine, ear or respiratory infections, sinusitis, stuffy or runny nose, abnormal hair texture, sensitivity to sunlight, migraine headache, eye pain or infection, blurred vision, puffy face, puffy hands or feet, enlarged liver, problem affecting ovary or vagina, pain in breast, difficulty in speaking, diabetes and swollen glands.

Very rarely sarcoidosis (a disease characterised by persistent fever, weight loss, joint pain and swelling, skin lesions and swollen glands) has been reported. Loss of consciousness has occurred very rarely with alpha interferons, mostly in elderly patients treated at high doses. Cases of stroke (cerebrovascular events) have been reported. Check with your doctor immediately if you have any of these symptoms or any other symptoms that are troubling.

Very rarely, PegIntron alone or in combination with ribavirin may cause aplastic anaemia.

When PegIntron is used alone, some of these effects are less likely to occur, and some have not occurred at all.

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

5. STORING PEGINTRON

Keep out of the reach and sight of children.

Store in a refrigerator (2°C - 8°C).

Do not use after the expiry date stated on the carton.
After reconstitution, use the reconstituted solution immediately or within 24 hours when stored at 2°C - 8°C (in a refrigerator).

Do not use PegIntron if you notice discolouration of the powder.

6. FURTHER INFORMATION

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

België/Belgique/Belgien
Rue de Stalle/Stallestraat 73
BE-1180 Bruxelles/Brussel/Brüssel
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Tlf: + 45-44 39 50 00

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Ísland
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Italia
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IT-20090 Segrate (Milano)
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HOW TO SELF-INJECT PEGINTRON?

The following instructions explain how to inject PegIntron yourself. Please read the instructions carefully and follow them step by step. Your doctor or his/her assistant will instruct you how to self-inject PegIntron. Do not attempt to inject yourself unless you are sure you understand the procedure and requirement of self-injection.

Preparation
Collect necessary items before you begin:
- a vial of PegIntron powder for injection;
- an ampoule of solvent for PegIntron (water for injections);
- a 1 ml syringe;
- a long needle (for example 0.8 × 40 mm [21 gauge 1.5 inch]) to be used to add water for injections to the PegIntron powder vial;
- a short needle (for example 0.3 × 13 mm [30 gauge 0.5 inch]) for the subcutaneous injection;
- a cleansing swab.

Wash your hands carefully.

Reconstituting PegIntron powder for injection
Before reconstitution, PegIntron may appear either as a white, tablet-shaped solid that is whole or in pieces, or as a white powder.
Remove the protective cap from the PegIntron vial. Clean the rubber top of the vial with a cleansing swab. You can save the swab to clean the skin area where you will inject the dose. Remove the syringe from the wrapping. Do not touch the tip of the syringe. Take the long needle and place it firmly on to the tip of the syringe. Remove the needle guard without touching the needle and keep the syringe with the needle in your hand. Tap the top of the ampoule of solvent gently to make sure that all the liquid is at the bottom of the ampoule. Break off the top of the ampoule of solvent. Insert the needle in the ampoule of solvent and withdraw the total amount of solvent.

When the total amount of solvent is combined with the full amount of PegIntron powder, the solution will be at the correct concentration to measure your dose (i.e., the labelled amount is contained in 0.5 ml).

A small volume is lost during preparation of PegIntron for injection and when the dose is measured and injected. Therefore, each vial contains an excess amount of solvent and PegIntron powder to ensure delivery of the labelled dose in 0.5 ml of PegIntron, solution for injection.

To prepare the PegIntron solution, insert the needle through the rubber top of the PegIntron vial and gently place the needle tip against the glass wall of the vial without touching the cleaned top of the vial with your hands.
Inject the solvent **SLOWLY**, aiming the stream of liquid at the glass wall of the vial. It is best not to aim the stream directly at the white solid or powder, or to inject the liquid quickly, as this causes a greater amount of bubbles. The solution may appear cloudy or bubbly for a few minutes. This is to be expected and is not cause for concern.

To dissolve the entire contents, swirl the PegIntron vial with a gentle rotary motion leaving the needle and attached syringe in the vial. **Do not shake**, but gently turn the vial upside down until any powder at the top of the vial is dissolved. The contents should now be completely dissolved. Stand the vial upright and let any bubbles present in the solution rise to the top of the solution. Once the solution has settled and all bubbles have risen to the top of the solution, you should have a clear solution with a small ring of tiny bubbles around the top. Now you can withdraw your dose from the vial. Use this solution immediately. If it cannot be used immediately, the solution may be refrigerated for up to 24 hours.

Measuring the dose of PegIntron from the reconstituted powder for injection
Turn the vial and the syringe upside down in one hand. Be sure the tip of needle is in the PegIntron reconstituted solution. Your other hand will be free to move the plunger. Pull back on the plunger

slowly to draw just more than the dose prescribed by your doctor into the syringe.
Hold the syringe with the needle in the vial pointing up, remove the syringe from the long needle leaving the needle in the vial and without touching the tip of the syringe. Take the short needle and place it firmly on to the tip of the syringe. Remove the needle guard from the syringe needle and check for air bubbles in the syringe. If you see any bubbles, pull the plunger slightly back; tap the syringe gently, with the needle pointing upwards, until the bubbles disappear. Push up the plunger slowly back to the correct dose. Replace the needle guard and place the syringe with the needle on a flat surface.

Be sure the solution is at room temperature up to 25°C. If the solution is cold, warm the syringe between your palms. Inspect visually the reconstituted solution prior to administration: do not use if discolouration or particulate matter is present. You are now ready to inject the dose.

Injecting the solution
Select the injection site. The best sites for injection are tissues with a layer of fat between skin and muscle: thigh, outer surface of the upper arm (you may need the assistance of another person to use this site), abdomen (except the navel or waistline). If you are exceptionally thin, use only the thigh or outer surface of the arm for injection.
Change your injection site each time.

Cleanse and disinfect the skin where the injection is to be made. Wait for the area to dry. Remove the needle guard. With one hand, pinch a fold of loose skin. With your other hand, hold the syringe as you would a pencil. Insert the needle into the pinched skin at an angle of approximately 45°. After the needle is in, remove the hand used to pinch the skin and use it to hold the syringe barrel. Pull back the plunger very slightly with one hand. If blood comes into the syringe, the needle has entered a blood vessel. Do not inject into this site; withdraw the needle and repeat the procedure. Inject the solution by pushing the plunger all the way down gently.
Pull the needle straight out of the skin. Press the injection site with a small bandage or sterile gauze if necessary for several seconds. Do not massage the injection site. If there is bleeding, cover with an adhesive bandage.
The vial, ampoule and injection materials intended for single use must be discarded. Dispose of the syringe and needles safely in a closed container.

PACKAGE LEAFLET

Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

In this leaflet:

PegIntron 80 micrograms powder and solvent for solution for injection
peginterferon alfa-2b (conjugation of recombinant interferon alfa-2b with monomethoxy polyethylene glycol)

- The active substance is peginterferon alfa-2b, 80 micrograms/0.5 ml.
- The other ingredients are:
  Powder: disodium phosphate, anhydrous; sodium dihydrogen phosphate dihydrate, sucrose and polysorbate 80;
  Solvent: water for injections 0.7 ml/ampoule.

Marketing Authorisation Holder: SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

Manufacturer: SP (Brinny) Company, Innishannon, County Cork, Ireland

1. WHAT PEGINTRON IS AND WHAT IT IS USED FOR

The pharmaceutical form is: powder and solvent for solution for injection.
The white powder is contained in a 2 ml glass vial and the clear and colourless solvent is presented in a 2 ml glass ampoule.

PegIntron 80 micrograms is available in different pack sizes:
- 1 vial of powder for solution for injection and 1 ampoule of solvent for parenteral use;
- 1 vial of powder for solution for injection, 1 ampoule of solvent for parenteral use, 1 injection syringe, 2 injection needles and 1 cleansing swab;
- 4 vials of powder for solution for injection and 4 ampoules of solvent for parenteral use;
- 4 vials of powder for solution for injection, 4 ampoules of solvent for parenteral use, 4 injection syringes, 8 injection needles and 4 cleansing swabs;
- 6 vials of powder for solution for injection and 6 ampoules of solvent for parenteral use;
- 12 vials of powder for solution for injection, 12 ampoules of solvent for parenteral use, 12 injection syringes, 24 injection needles and 12 cleansing swabs.

Not all pack sizes may be marketed.

Interferons modify the response of the body's immune system to help fight infections and severe diseases. PegIntron, which contains an interferon, is used for the treatment of chronic hepatitis C, a viral infection of the liver.

PegIntron is best used for this treatment in combination with ribavirin.

PegIntron is used alone in case of intolerance or contraindication to ribavirin.

2. BEFORE YOU USE PEGINTRON

PegIntron is not recommended for use in patients under the age of 18 years.

Do not use PegIntron:
- If you are hypersensitive (allergic) to peginterferon alfa-2b or any of the other ingredients of PegIntron.
- If you are hypersensitive (allergic) to any interferon.
- If you are pregnant or breast feeding.
- If you have had severe heart problems, or if you have heart disease that has not been well controlled during the past 6 months.
- If you have severe medical conditions that leave you very weak, including severe kidney disease.
- If you have autoimmune hepatitis or any other problem with your immune system; if you are taking medicine that suppresses your immune system (your immune system protects you against infection and some diseases).
- If you have advanced, uncontrolled liver disease (other than hepatitis C).
- If you have thyroid disease that is not well controlled with medicines.
- If you have a condition that causes convulsions (seizures, or "fits").

Take special care with PegIntron:
- If you develop symptoms of a severe allergic reaction (such as difficulty in breathing, wheezing, or hives) while on this medication, seek medical help immediately.
- If you ever had a heart attack or a heart problem.
- If you have ever been treated for depression or any other nervous or mental disorder.
- If you have had a problem with your liver (other than hepatitis C).
- If you develop symptoms associated with a cold or other respiratory infection, such as fever, cough, or any difficulty in breathing, tell your doctor.
- If you are diabetic, your doctor may ask you to have an eye examination.
- If you have had any serious illness affecting your breathing or your blood.
- If you have psoriasis, it may become worse while you are using PegIntron.
- If you are planning to become pregnant, discuss this with your doctor before starting to use PegIntron.
- If you are also being treated for HIV, please see **Using other medicines**.
- If you have had a severe nervous or mental disorder.
- If you have received an organ transplant, either kidney or liver, interferon treatment may increase the risk of rejection. Be sure to discuss this with your doctor.

While being treated with PegIntron
Your doctor may want you to drink extra fluids to help prevent low blood pressure.

Pregnancy
Ask your doctor or pharmacist for advice before taking any medicine. Do not use PegIntron during pregnancy. The effect on human pregnancy is not known.

Breast-feeding
Ask your doctor or pharmacist for advice before taking any medicine. It is not known whether this product is present in human milk. Therefore, do not breast-feed an infant if you are taking PegIntron.

Driving and using machines:
Do not drive or operate any tools or machines if you feel tired, sleepy or confused while taking PegIntron.

Using other medicines:

Please inform your doctor or pharmacist if you are taking or have recently taken any other medicines, even those not prescribed.

Important information about some of the ingredients of PegIntron:
This medicinal product contains less than 1 mmol sodium (23 mg) per 0.7 ml, i.e., essentially "sodium-free".

Patients who also have HIV infection:
Lactic acidosis and worsening liver function are side effects associated with Highly Active Anti-Retroviral Therapy (HAART), an HIV treatment. If you are receiving HAART, the addition of PegIntron and ribavirin may increase your risk of lactic acidosis and of liver failure. Your doctor will monitor you for signs and symptoms of these conditions. (Please be sure to read the ribavirin Patient Leaflet also).

3. HOW TO USE PEGINTRON

Your doctor has prescribed PegIntron specifically for you and your current condition; do not share this medicine with anyone else.

Your doctor has determined your dose of PegIntron based on your weight. If necessary, the dose may be changed during treatment.

Combination treatment
PegIntron, when given with ribavirin capsules, is usually given at a dose of 1.5 microgram/kg once a week.

Ribavirin capsules are taken every day, morning and evening. The number of ribavirin capsules you take depends on your weight.
- If you weigh less than 65 kg, take 2 capsules in the morning and 2 in the evening (total of 800 mg each day).
- If you weigh between 65 and 85 kg, take 2 capsules in the morning and 3 in the evening (total of 1,000 mg each day).
- If you weigh more than 85 kg, take 3 capsules in the morning and 3 in the evening (total 1,200 mg each day).

The combination treatment is continued for at least 6 months, and sometimes for one year.

PegIntron alone:
PegIntron, when given alone, is usually given at a dose of 0.5 or 1.0 microgram/kg once a week, for at least 6 months, and possibly for 1 year.

All patients:
If you are injecting PegIntron yourself, please be sure that the dose that has been prescribed for you is clearly provided on the package of medicine you receive.

If you have the impression that the effect of PegIntron is too strong or too weak, talk to your doctor or pharmacist.

PegIntron is intended for subcutaneous use. This means that it is injected through a short injection needle into the fatty tissue just under your skin. If you are injecting this medicine yourself, you will be instructed how to prepare and give the injection. Detailed instructions for subcutaneous administration are provided with this leaflet (see How to self-inject PegIntron at the end of the package leaflet).

Prepare the dose just before you intend to inject it and use it immediately. Look carefully at the reconstituted solution prior to administration. Do not use if there is discolouration of the reconstituted solution or if particulate matter is present. Discard any solution that is left in the vial after you give

yourself the injection.

Inject PegIntron once each week on the same day. Injecting it at the same time of day each week will help you not to forget to take it.

Use PegIntron exactly as prescribed by your doctor. Do not exceed the recommended dosage, and take it for as long as prescribed.

If you use more PegIntron than you should:
Tell your doctor or healthcare professional as soon as possible.

If you forget to take PegIntron:
Take the dose as soon as you remember, then continue your treatment as usual.
Do not take a double dose to make up for forgotten individual doses. Contact your doctor or pharmacist if needed.

4. POSSIBLE SIDE EFFECTS

Like all medicines, PegIntron can have side effects. Although not all of these side effects may occur, they may need medical attention if they do.

Check with your doctor immediately if any of the following side effects occur: chest pain; changes in the way your heart beats; breathing problems, (including shortness of breath), confusion; feeling depressed, wanting to harm yourself, hallucinations, numbness or tingling feeling; dizziness, convulsion ("fit"); trouble sleeping, thinking or concentrating; difficulty remaining alert, severe stomach pain or cramps; blood or clots in stool (or black, tarry stool); fever or chills beginning after a few weeks of treatment, pain in your lower back or side; difficulty or inability to pass urine, painful or inflamed muscles (sometimes severe); problems with your eyes or your eyesight or hearing; severe or painful reddening of your skin or mucous membrane, severe bleeding from your nose. Your doctor will test your blood to ensure that your white blood cell (cells that fight infection) and red blood cell (cells that carry oxygen) counts, platelets (blood clotting cells) and other laboratory values are at acceptable levels.

Some people get depressed when taking PegIntron alone or in combination treatment with ribavirin, and in some cases people had suicidal thoughts or aggressive behaviour. Some patients have actually committed suicide. Be sure to seek emergency care if you notice that you are becoming depressed or have suicidal thoughts or change in your behaviour. You may want to consider asking a family member or close friend to help you stay alert to signs of depression or changes in your behaviour.

The most common side effects with the combination of PegIntron and ribavirin capsules are irritation or redness (and rarely, skin damage) at the site of injection, headache, tired feeling, shaking chills, fever, flu-like symptoms, weakness, loss of weight, nausea, loss of appetite, diarrhoea or loose stools, stomach pain, vomiting, muscle aches, pain in joints and muscles, feeling depressed, irritability, trouble falling asleep or staying asleep, feeling anxious or nervous, difficulty concentrating, mood swings, hair loss, itching, dry skin, sore throat, coughing, difficult breathing, dizziness, virus infection, rash, and dry mouth.

Other common side effects that may occur with combination treatment are increased sweating, chest pain, pain on the right side around your ribs, numbness, pain or tingling feeling, change in thyroid gland activity (which may make you feel tired or, less commonly, energetic), stomach upset, rapid heart rate, agitation, nervousness, difficult or irregular menstrual period.

Less common are pain at the place of injection, flushing, low or high blood pressure, dry or teary eyes, redness of skin or skin disorders, psoriasis, hives, nail disorder, feeling unwell, feeling faint, poor coordination, confusion, increased or decreased sensitivity to touch, tense muscles, arthritis, bruising, loss of interest in activities including sex, sexual problem, unusual dreams, shaky hands, vertigo (spinning feeling), increased appetite, heartburn, intestinal gas (flatus), constipation, hemorrhoids, red or bleeding

gums, redness or sores in mouth, change in taste, changes in hearing or ringing in ears, thirst, aggressive or changed behaviour, feeling sleepy, cold sores, fungal or bacterial infections, irritation of prostate gland, increased need to pass urine, ear or respiratory infections, sinusitis, stuffy or runny nose, abnormal hair texture, sensitivity to sunlight, migraine headache, eye pain or infection, blurred vision, puffy face, puffy hands or feet, enlarged liver, problem affecting ovary or vagina, pain in breast, difficulty in speaking, diabetes and swollen glands.

Very rarely sarcoidosis (a disease characterised by persistent fever, weight loss, joint pain and swelling, skin lesions and swollen glands) has been reported. Loss of consciousness has occurred very rarely with alpha interferons, mostly in elderly patients treated at high doses. Cases of stroke (cerebrovascular events) have been reported. Check with your doctor immediately if you have any of these symptoms or any other symptoms that are troubling.

Very rarely, PegIntron alone or in combination with ribavirin may cause aplastic anaemia.

When PegIntron is used alone, some of these effects are less likely to occur, and some have not occurred at all.

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

5. STORING PEGINTRON

Keep out of the reach and sight of children.

Store in a refrigerator (2°C - 8°C).

Do not use after the expiry date stated on the carton.
After reconstitution, use the reconstituted solution immediately or within 24 hours when stored at 2°C - 8°C (in a refrigerator).

Do not use PegIntron if you notice discolouration of the powder.

6. FURTHER INFORMATION

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

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HOW TO SELF-INJECT PEGINTRON?

The following instructions explain how to inject PegIntron yourself. Please read the instructions carefully and follow them step by step. Your doctor or his/her assistant will instruct you how to self-inject PegIntron. Do not attempt to inject yourself unless you are sure you understand the procedure and requirement of self-injection.

Preparation
Collect necessary items before you begin:
- a vial of PegIntron powder for injection;
- an ampoule of solvent for PegIntron (water for injections);
- a 1 ml syringe;
- a long needle (for example 0.8 × 40 mm [21 gauge 1.5 inch]) to be used to add water for injections to the PegIntron powder vial;
- a short needle (for example 0.3 × 13 mm [30 gauge 0.5 inch]) for the subcutaneous injection;
- a cleansing swab.

Wash your hands carefully.

Reconstituting PegIntron powder for injection
Before reconstitution, PegIntron may appear either as a white, tablet-shaped solid that is whole or in pieces, or as a white powder.
Remove the protective cap from the PegIntron vial. Clean the rubber top of the vial with a cleansing swab. You can save the swab to clean the skin area where you will inject the dose. Remove the syringe from the wrapping. Do not touch the tip of the syringe. Take the long needle and place it firmly on to the tip of the syringe. Remove the needle guard without touching the needle and keep the syringe with the needle in your hand. Tap the top of the ampoule of solvent gently to make sure that all the liquid is at the bottom of the ampoule. Break off the top of the ampoule of solvent. Insert the needle in the ampoule of solvent and withdraw the total amount of solvent.

When the total amount of solvent is combined with the full amount of PegIntron powder, the solution will be at the correct concentration to measure your dose (i.e., the labelled amount is contained in 0.5 ml).

A small volume is lost during preparation of PegIntron for injection and when the dose is measured and injected. Therefore, each vial contains an excess amount of solvent and PegIntron powder to ensure delivery of the labelled dose in 0.5 ml of PegIntron, solution for injection.

To prepare the PegIntron solution, insert the needle through the rubber top of the PegIntron vial and gently place the needle tip against the glass wall of the vial without touching the cleaned top of the vial with your hands.
Inject the solvent **SLOWLY**, aiming the stream of liquid at the glass wall of the vial. It is best not to aim the stream directly at the white solid or powder, or to inject the liquid quickly, as this causes a greater amount of bubbles. The solution may appear cloudy or bubbly for a few minutes. This is to be expected and is not cause for concern.

To dissolve the entire contents, swirl the PegIntron vial with a gentle rotary motion leaving the needle and attached syringe in the vial. **Do not shake**, but gently turn the vial upside down until any powder at the top of the vial is dissolved. The contents should now be completely dissolved. Stand the vial upright and let any bubbles present in the solution rise to the top of the solution. Once the solution has settled and all bubbles have risen to the top of the solution, you should have a clear solution with a small ring of tiny bubbles around the top. Now you can withdraw your dose from the vial. Use this solution immediately. If it cannot be used immediately, the solution may be refrigerated for up to 24 hours.

Measuring the dose of PegIntron from the reconstituted powder for injection
Turn the vial and the syringe upside down in one hand. Be sure the tip of needle is in the PegIntron reconstituted solution. Your other hand will be free to move the plunger. Pull back on the plunger

slowly to draw just more than the dose prescribed by your doctor into the syringe.
Hold the syringe with the needle in the vial pointing up, remove the syringe from the long needle leaving the needle in the vial and without touching the tip of the syringe. Take the short needle and place it firmly on to the tip of the syringe. Remove the needle guard from the syringe needle and check for air bubbles in the syringe. If you see any bubbles, pull the plunger slightly back; tap the syringe gently, with the needle pointing upwards, until the bubbles disappear. Push up the plunger slowly back to the correct dose. Replace the needle guard and place the syringe with the needle on a flat surface.

Be sure the solution is at room temperature up to 25°C. If the solution is cold, warm the syringe between your palms. Inspect visually the reconstituted solution prior to administration: do not use if discolouration or particulate matter is present. You are now ready to inject the dose.

Injecting the solution
Select the injection site. The best sites for injection are tissues with a layer of fat between skin and muscle: thigh, outer surface of the upper arm (you may need the assistance of another person to use this site), abdomen (except the navel or waistline). If you are exceptionally thin, use only the thigh or outer surface of the arm for injection.
Change your injection site each time.

Cleanse and disinfect the skin where the injection is to be made. Wait for the area to dry. Remove the needle guard. With one hand, pinch a fold of loose skin. With your other hand, hold the syringe as you would a pencil. Insert the needle into the pinched skin at an angle of approximately 45°. After the needle is in, remove the hand used to pinch the skin and use it to hold the syringe barrel. Pull back the plunger very slightly with one hand. If blood comes into the syringe, the needle has entered a blood vessel. Do not inject into this site; withdraw the needle and repeat the procedure. Inject the solution by pushing the plunger all the way down gently.
Pull the needle straight out of the skin. Press the injection site with a small bandage or sterile gauze if necessary for several seconds. Do not massage the injection site. If there is bleeding, cover with an adhesive bandage.
The vial, ampoule and injection materials intended for single use must be discarded. Dispose of the syringe and needles safely in a closed container.

PACKAGE LEAFLET

Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

In this leaflet:

PegIntron 100 micrograms powder and solvent for solution for injection
peginterferon alfa-2b (conjugation of recombinant interferon alfa-2b with monomethoxy polyethylene glycol)

- The active substance is peginterferon alfa-2b, 100 micrograms/0.5 ml.
- The other ingredients are:
  Powder: disodium phosphate, anhydrous; sodium dihydrogen phosphate dihydrate, sucrose and polysorbate 80;
  Solvent: water for injections 0.7 ml/ampoule.

Marketing Authorisation Holder: SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

Manufacturer: SP (Brinny) Company, Innishannon, County Cork, Ireland

1. WHAT PEGINTRON IS AND WHAT IT IS USED FOR

The pharmaceutical form is: powder and solvent for solution for injection.
The white powder is contained in a 2 ml glass vial and the clear and colourless solvent is presented in a 2 ml glass ampoule.

PegIntron 100 micrograms is available in different pack sizes:
- 1 vial of powder for solution for injection and 1 ampoule of solvent for parenteral use;
- 1 vial of powder for solution for injection, 1 ampoule of solvent for parenteral use, 1 injection syringe, 2 injection needles and 1 cleansing swab;
- 4 vials of powder for solution for injection and 4 ampoules of solvent for parenteral use;
- 4 vials of powder for solution for injection, 4 ampoules of solvent for parenteral use, 4 injection syringes, 8 injection needles and 4 cleansing swabs;
- 6 vials of powder for solution for injection and 6 ampoules of solvent for parenteral use;
- 12 vials of powder for solution for injection, 12 ampoules of solvent for parenteral use, 12 injection syringes, 24 injection needles and 12 cleansing swabs.

Not all pack sizes may be marketed.

Interferons modify the response of the body's immune system to help fight infections and severe diseases. PegIntron, which contains an interferon, is used for the treatment of chronic hepatitis C, a viral infection of the liver.

PegIntron is best used for this treatment in combination with ribavirin.

PegIntron is used alone in case of intolerance or contraindication to ribavirin.

2. BEFORE YOU USE PEGINTRON

PegIntron is not recommended for use in patients under the age of 18 years.

Do not use PegIntron:
- If you are hypersensitive (allergic) to peginterferon alfa-2b or any of the other ingredients of PegIntron.
- If you are hypersensitive (allergic) to any interferon.
- If you are pregnant or breast feeding.
- If you have had severe heart problems, or if you have heart disease that has not been well controlled during the past 6 months.
- If you have severe medical conditions that leave you very weak, including severe kidney disease.
- If you have autoimmune hepatitis or any other problem with your immune system; if you are taking medicine that suppresses your immune system (your immune system protects you against infection and some diseases).
- If you have advanced, uncontrolled liver disease (other than hepatitis C).
- If you have thyroid disease that is not well controlled with medicines.
- If you have a condition that causes convulsions (seizures, or "fits").

Take special care with PegIntron:
- If you develop symptoms of a severe allergic reaction (such as difficulty in breathing, wheezing, or hives) while on this medication, seek medical help immediately.
- If you ever had a heart attack or a heart problem.
- If you have ever been treated for depression or any other nervous or mental disorder.
- If you have had a problem with your liver (other than hepatitis C).
- If you develop symptoms associated with a cold or other respiratory infection, such as fever, cough, or any difficulty in breathing, tell your doctor.
- If you are diabetic, your doctor may ask you to have an eye examination.
- If you have had any serious illness affecting your breathing or your blood.
- If you have psoriasis, it may become worse while you are using PegIntron.
- If you are planning to become pregnant, discuss this with your doctor before starting to use PegIntron.
- If you are also being treated for HIV, please see **Using other medicines**.
- If you have had a severe nervous or mental disorder.
- If you have received an organ transplant, either kidney or liver, interferon treatment may increase the risk of rejection. Be sure to discuss this with your doctor.

While being treated with PegIntron
Your doctor may want you to drink extra fluids to help prevent low blood pressure.

Pregnancy
Ask your doctor or pharmacist for advice before taking any medicine. Do not use PegIntron during pregnancy. The effect on human pregnancy is not known.

Breast-feeding
Ask your doctor or pharmacist for advice before taking any medicine. It is not known whether this product is present in human milk. Therefore, do not breast-feed an infant if you are taking PegIntron.

Driving and using machines:
Do not drive or operate any tools or machines if you feel tired, sleepy or confused while taking PegIntron.

Using other medicines:

Please inform your doctor or pharmacist if you are taking or have recently taken any other medicines, even those not prescribed.

Important information about some of the ingredients of PegIntron:
This medicinal product contains less than 1 mmol sodium (23 mg) per 0.7 ml, i.e., essentially "sodium-free".

Patients who also have HIV infection:
Lactic acidosis and worsening liver function are side effects associated with Highly Active Anti-Retroviral Therapy (HAART), an HIV treatment. If you are receiving HAART, the addition of PegIntron and ribavirin may increase your risk of lactic acidosis and of liver failure. Your doctor will monitor you for signs and symptoms of these conditions. (Please be sure to read the ribavirin Patient Leaflet also).

3. HOW TO USE PEGINTRON

Your doctor has prescribed PegIntron specifically for you and your current condition; do not share this medicine with anyone else.

Your doctor has determined your dose of PegIntron based on your weight. If necessary, the dose may be changed during treatment.

Combination treatment
PegIntron, when given with ribavirin capsules, is usually given at a dose of 1.5 microgram/kg once a week.

Ribavirin capsules are taken every day, morning and evening. The number of ribavirin capsules you take depends on your weight.
- If you weigh less than 65 kg, take 2 capsules in the morning and 2 in the evening (total of 800 mg each day).
- If you weigh between 65 and 85 kg, take 2 capsules in the morning and 3 in the evening (total of 1,000 mg each day).
- If you weigh more than 85 kg, take 3 capsules in the morning and 3 in the evening (total 1,200 mg each day).

The combination treatment is continued for at least 6 months, and sometimes for one year.

PegIntron alone:
PegIntron, when given alone, is usually given at a dose of 0.5 or 1.0 microgram/kg once a week, for at least 6 months, and possibly for 1 year.

All patients:
If you are injecting PegIntron yourself, please be sure that the dose that has been prescribed for you is clearly provided on the package of medicine you receive.

If you have the impression that the effect of PegIntron is too strong or too weak, talk to your doctor or pharmacist.

PegIntron is intended for subcutaneous use. This means that it is injected through a short injection needle into the fatty tissue just under your skin. If you are injecting this medicine yourself, you will be instructed how to prepare and give the injection. Detailed instructions for subcutaneous administration are provided with this leaflet (see How to self-inject PegIntron at the end of the package leaflet).

Prepare the dose just before you intend to inject it and use it immediately. Look carefully at the reconstituted solution prior to administration. Do not use if there is discolouration of the reconstituted solution or if particulate matter is present. Discard any solution that is left in the vial after you give

yourself the injection.

Inject PegIntron once each week on the same day. Injecting it at the same time of day each week will help you not to forget to take it.

Use PegIntron exactly as prescribed by your doctor. Do not exceed the recommended dosage, and take it for as long as prescribed.

If you use more PegIntron than you should:
Tell your doctor or healthcare professional as soon as possible.

If you forget to take PegIntron:
Take the dose as soon as you remember, then continue your treatment as usual.
Do not take a double dose to make up for forgotten individual doses. Contact your doctor or pharmacist if needed.

4. POSSIBLE SIDE EFFECTS

Like all medicines, PegIntron can have side effects. Although not all of these side effects may occur, they may need medical attention if they do.

Check with your doctor immediately if any of the following side effects occur: chest pain; changes in the way your heart beats; breathing problems, (including shortness of breath), confusion; feeling depressed, wanting to harm yourself, hallucinations, numbness or tingling feeling; dizziness, convulsion ("fit"); trouble sleeping, thinking or concentrating; difficulty remaining alert, severe stomach pain or cramps; blood or clots in stool (or black, tarry stool); fever or chills beginning after a few weeks of treatment, pain in your lower back or side; difficulty or inability to pass urine, painful or inflamed muscles (sometimes severe); problems with your eyes or your eyesight or hearing; severe or painful reddening of your skin or mucous membrane, severe bleeding from your nose. Your doctor will test your blood to ensure that your white blood cell (cells that fight infection) and red blood cell (cells that carry oxygen) counts, platelets (blood clotting cells) and other laboratory values are at acceptable levels.

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The most common side effects with the combination of PegIntron and ribavirin capsules are irritation or redness (and rarely, skin damage) at the site of injection, headache, tired feeling, shaking chills, fever, flu-like symptoms, weakness, loss of weight, nausea, loss of appetite, diarrhoea or loose stools, stomach pain, vomiting, muscle aches, pain in joints and muscles, feeling depressed, irritability, trouble falling asleep or staying asleep, feeling anxious or nervous, difficulty concentrating, mood swings, hair loss, itching, dry skin, sore throat, coughing, difficult breathing, dizziness, virus infection, rash, and dry mouth.

Other common side effects that may occur with combination treatment are increased sweating, chest pain, pain on the right side around your ribs, numbness, pain or tingling feeling, change in thyroid gland activity (which may make you feel tired or, less commonly, energetic), stomach upset, rapid heart rate, agitation, nervousness, difficult or irregular menstrual period.

Less common are pain at the place of injection, flushing, low or high blood pressure, dry or teary eyes, redness of skin or skin disorders, psoriasis, hives, nail disorder, feeling unwell, feeling faint, poor coordination, confusion, increased or decreased sensitivity to touch, tense muscles, arthritis, bruising, loss of interest in activities including sex, sexual problem, unusual dreams, shaky hands, vertigo (spinning feeling), increased appetite, heartburn, intestinal gas (flatus), constipation, hemorrhoids, red or bleeding

gums, redness or sores in mouth, change in taste, changes in hearing or ringing in ears, thirst, aggressive or changed behaviour, feeling sleepy, cold sores, fungal or bacterial infections, irritation of prostate gland, increased need to pass urine, ear or respiratory infections, sinusitis, stuffy or runny nose, abnormal hair texture, sensitivity to sunlight, migraine headache, eye pain or infection, blurred vision, puffy face, puffy hands or feet, enlarged liver, problem affecting ovary or vagina, pain in breast, difficulty in speaking, diabetes and swollen glands.

Very rarely sarcoidosis (a disease characterised by persistent fever, weight loss, joint pain and swelling, skin lesions and swollen glands) has been reported. Loss of consciousness has occurred very rarely with alpha interferons, mostly in elderly patients treated at high doses. Cases of stroke (cerebrovascular events) have been reported. Check with your doctor immediately if you have any of these symptoms or any other symptoms that are troubling.

Very rarely, PegIntron alone or in combination with ribavirin may cause aplastic anaemia.

When PegIntron is used alone, some of these effects are less likely to occur, and some have not occurred at all.

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

5. STORING PEGINTRON

Keep out of the reach and sight of children.

Store in a refrigerator (2°C - 8°C).

Do not use after the expiry date stated on the carton.
After reconstitution, use the reconstituted solution immediately or within 24 hours when stored at 2°C - 8°C (in a refrigerator).

Do not use PegIntron if you notice discolouration of the powder.

6. FURTHER INFORMATION

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HOW TO SELF-INJECT PEGINTRON?

The following instructions explain how to inject PegIntron yourself. Please read the instructions carefully and follow them step by step. Your doctor or his/her assistant will instruct you how to self-inject PegIntron. Do not attempt to inject yourself unless you are sure you understand the procedure and requirement of self-injection.

Preparation
Collect necessary items before you begin:
- a vial of PegIntron powder for injection;
- an ampoule of solvent for PegIntron (water for injections);
- a 1 ml syringe;
- a long needle (for example 0.8 × 40 mm [21 gauge 1.5 inch]) to be used to add water for injections to the PegIntron powder vial;
- a short needle (for example 0.3 × 13 mm [30 gauge 0.5 inch]) for the subcutaneous injection;
- a cleansing swab.

Wash your hands carefully.

Reconstituting PegIntron powder for injection
Before reconstitution, PegIntron may appear either as a white, tablet-shaped solid that is whole or in pieces, or as a white powder.
Remove the protective cap from the PegIntron vial. Clean the rubber top of the vial with a cleansing swab. You can save the swab to clean the skin area where you will inject the dose. Remove the syringe from the wrapping. Do not touch the tip of the syringe. Take the long needle and place it firmly on to the tip of the syringe. Remove the needle guard without touching the needle and keep the syringe with the needle in your hand. Tap the top of the ampoule of solvent gently to make sure that all the liquid is at the bottom of the ampoule. Break off the top of the ampoule of solvent. Insert the needle in the ampoule of solvent and withdraw the total amount of solvent.

When the total amount of solvent is combined with the full amount of PegIntron powder, the solution will be at the correct concentration to measure your dose (i.e., the labelled amount is contained in 0.5 ml).

A small volume is lost during preparation of PegIntron for injection and when the dose is measured and injected. Therefore, each vial contains an excess amount of solvent and PegIntron powder to ensure delivery of the labelled dose in 0.5 ml of PegIntron, solution for injection.

To prepare the PegIntron solution, insert the needle through the rubber top of the PegIntron vial and gently place the needle tip against the glass wall of the vial without touching the cleaned top of the vial with your hands.
Inject the solvent **SLOWLY**, aiming the stream of liquid at the glass wall of the vial. It is best not to aim the stream directly at the white solid or powder, or to inject the liquid quickly, as this causes a greater amount of bubbles. The solution may appear cloudy or bubbly for a few minutes. This is to be expected and is not cause for concern.

To dissolve the entire contents, swirl the PegIntron vial with a gentle rotary motion leaving the needle and attached syringe in the vial. **Do not shake**, but gently turn the vial upside down until any powder at the top of the vial is dissolved. The contents should now be completely dissolved. Stand the vial upright and let any bubbles present in the solution rise to the top of the solution. Once the solution has settled and all bubbles have risen to the top of the solution, you should have a clear solution with a small ring of tiny bubbles around the top. Now you can withdraw your dose from the vial. Use this solution immediately. If it cannot be used immediately, the solution may be refrigerated for up to 24 hours.

Measuring the dose of PegIntron from the reconstituted powder for injection
Turn the vial and the syringe upside down in one hand. Be sure the tip of needle is in the PegIntron reconstituted solution. Your other hand will be free to move the plunger. Pull back on the plunger

slowly to draw just more than the dose prescribed by your doctor into the syringe.
Hold the syringe with the needle in the vial pointing up, remove the syringe from the long needle leaving the needle in the vial and without touching the tip of the syringe. Take the short needle and place it firmly on to the tip of the syringe. Remove the needle guard from the syringe needle and check for air bubbles in the syringe. If you see any bubbles, pull the plunger slightly back; tap the syringe gently, with the needle pointing upwards, until the bubbles disappear. Push up the plunger slowly back to the correct dose. Replace the needle guard and place the syringe with the needle on a flat surface.

Be sure the solution is at room temperature up to 25°C. If the solution is cold, warm the syringe between your palms. Inspect visually the reconstituted solution prior to administration: do not use if discolouration or particulate matter is present. You are now ready to inject the dose.

Injecting the solution
Select the injection site. The best sites for injection are tissues with a layer of fat between skin and muscle: thigh, outer surface of the upper arm (you may need the assistance of another person to use this site), abdomen (except the navel or waistline). If you are exceptionally thin, use only the thigh or outer surface of the arm for injection.
Change your injection site each time.

Cleanse and disinfect the skin where the injection is to be made. Wait for the area to dry. Remove the needle guard. With one hand, pinch a fold of loose skin. With your other hand, hold the syringe as you would a pencil. Insert the needle into the pinched skin at an angle of approximately 45°. After the needle is in, remove the hand used to pinch the skin and use it to hold the syringe barrel. Pull back the plunger very slightly with one hand. If blood comes into the syringe, the needle has entered a blood vessel. Do not inject into this site; withdraw the needle and repeat the procedure. Inject the solution by pushing the plunger all the way down gently.
Pull the needle straight out of the skin. Press the injection site with a small bandage or sterile gauze if necessary for several seconds. Do not massage the injection site. If there is bleeding, cover with an adhesive bandage.
The vial, ampoule and injection materials intended for single use must be discarded. Dispose of the syringe and needles safely in a closed container.

PACKAGE LEAFLET

Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

In this leaflet:

PegIntron 120 micrograms powder and solvent for solution for injection
peginterferon alfa-2b (conjugation of recombinant interferon alfa-2b with monomethoxy polyethylene glycol)

- The active substance is peginterferon alfa-2b, 120 micrograms/0.5 ml.
- The other ingredients are:
  Powder: disodium phosphate, anhydrous; sodium dihydrogen phosphate dihydrate, sucrose and polysorbate 80;
  Solvent: water for injections 0.7 ml/ampoule.

Marketing Authorisation Holder: SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

Manufacturer: SP (Brinny) Company, Innishannon, County Cork, Ireland

1. WHAT PEGINTRON IS AND WHAT IT IS USED FOR

The pharmaceutical form is: powder and solvent for solution for injection.
The white powder is contained in a 2 ml glass vial and the clear and colourless solvent is presented in a 2 ml glass ampoule.

PegIntron 120 micrograms is available in different pack sizes:
- 1 vial of powder for solution for injection and 1 ampoule of solvent for parenteral use;
- 1 vial of powder for solution for injection, 1 ampoule of solvent for parenteral use, 1 injection syringe, 2 injection needles and 1 cleansing swab;
- 4 vials of powder for solution for injection and 4 ampoules of solvent for parenteral use;
- 4 vials of powder for solution for injection, 4 ampoules of solvent for parenteral use, 4 injection syringes, 8 injection needles and 4 cleansing swabs;
- 6 vials of powder for solution for injection and 6 ampoules of solvent for parenteral use;
- 12 vials of powder for solution for injection, 12 ampoules of solvent for parenteral use, 12 injection syringes, 24 injection needles and 12 cleansing swabs.

Not all pack sizes may be marketed.

Interferons modify the response of the body's immune system to help fight infections and severe diseases. PegIntron, which contains an interferon, is used for the treatment of chronic hepatitis C, a viral infection of the liver.

PegIntron is best used for this treatment in combination with ribavirin.

PegIntron is used alone in case of intolerance or contraindication to ribavirin.

2. BEFORE YOU USE PEGINTRON

PegIntron is not recommended for use in patients under the age of 18 years.

Do not use PegIntron:
- If you are hypersensitive (allergic) to peginterferon alfa-2b or any of the other ingredients of PegIntron.
- If you are hypersensitive (allergic) to any interferon.
- If you are pregnant or breast feeding.
- If you have had severe heart problems, or if you have heart disease that has not been well controlled during the past 6 months.
- If you have severe medical conditions that leave you very weak, including severe kidney disease.
- If you have autoimmune hepatitis or any other problem with your immune system; if you are taking medicine that suppresses your immune system (your immune system protects you against infection and some diseases).
- If you have advanced, uncontrolled liver disease (other than hepatitis C).
- If you have thyroid disease that is not well controlled with medicines.
- If you have a condition that causes convulsions (seizures, or "fits").

Take special care with PegIntron:
- If you develop symptoms of a severe allergic reaction (such as difficulty in breathing, wheezing, or hives) while on this medication, seek medical help immediately.
- If you ever had a heart attack or a heart problem.
- If you have ever been treated for depression or any other nervous or mental disorder.
- If you have had a problem with your liver (other than hepatitis C).
- If you develop symptoms associated with a cold or other respiratory infection, such as fever, cough, or any difficulty in breathing, tell your doctor.
- If you are diabetic, your doctor may ask you to have an eye examination.
- If you have had any serious illness affecting your breathing or your blood.
- If you have psoriasis, it may become worse while you are using PegIntron.
- If you are planning to become pregnant, discuss this with your doctor before starting to use PegIntron.
- If you are also being treated for HIV, please see **Using other medicines**.
- If you have had a severe nervous or mental disorder.
- If you have received an organ transplant, either kidney or liver, interferon treatment may increase the risk of rejection. Be sure to discuss this with your doctor.

While being treated with PegIntron
Your doctor may want you to drink extra fluids to help prevent low blood pressure.

Pregnancy
Ask your doctor or pharmacist for advice before taking any medicine. Do not use PegIntron during pregnancy. The effect on human pregnancy is not known.

Breast-feeding
Ask your doctor or pharmacist for advice before taking any medicine. It is not known whether this product is present in human milk. Therefore, do not breast-feed an infant if you are taking PegIntron.

Driving and using machines:
Do not drive or operate any tools or machines if you feel tired, sleepy or confused while taking PegIntron.

Using other medicines:

Please inform your doctor or pharmacist if you are taking or have recently taken any other medicines, even those not prescribed.

Important information about some of the ingredients of PegIntron:
This medicinal product contains less than 1 mmol sodium (23 mg) per 0.7 ml, i.e., essentially "sodium-free".

Patients who also have HIV infection:
Lactic acidosis and worsening liver function are side effects associated with Highly Active Anti-Retroviral Therapy (HAART), an HIV treatment. If you are receiving HAART, the addition of PegIntron and ribavirin may increase your risk of lactic acidosis and of liver failure. Your doctor will monitor you for signs and symptoms of these conditions. (Please be sure to read the ribavirin Patient Leaflet also).

3. HOW TO USE PEGINTRON

Your doctor has prescribed PegIntron specifically for you and your current condition; do not share this medicine with anyone else.

Your doctor has determined your dose of PegIntron based on your weight. If necessary, the dose may be changed during treatment.

Combination treatment
PegIntron, when given with ribavirin capsules, is usually given at a dose of 1.5 microgram/kg once a week.

Ribavirin capsules are taken every day, morning and evening. The number of ribavirin capsules you take depends on your weight.
- If you weigh less than 65 kg, take 2 capsules in the morning and 2 in the evening (total of 800 mg each day).
- If you weigh between 65 and 85 kg, take 2 capsules in the morning and 3 in the evening (total of 1,000 mg each day).
- If you weigh more than 85 kg, take 3 capsules in the morning and 3 in the evening (total 1,200 mg each day).

The combination treatment is continued for at least 6 months, and sometimes for one year.

PegIntron alone:
PegIntron, when given alone, is usually given at a dose of 0.5 or 1.0 microgram/kg once a week, for at least 6 months, and possibly for 1 year.

All patients:
If you are injecting PegIntron yourself, please be sure that the dose that has been prescribed for you is clearly provided on the package of medicine you receive.

If you have the impression that the effect of PegIntron is too strong or too weak, talk to your doctor or pharmacist.

PegIntron is intended for subcutaneous use. This means that it is injected through a short injection needle into the fatty tissue just under your skin. If you are injecting this medicine yourself, you will be instructed how to prepare and give the injection. Detailed instructions for subcutaneous administration are provided with this leaflet (see How to self-inject PegIntron at the end of the package leaflet).

Prepare the dose just before you intend to inject it and use it immediately. Look carefully at the reconstituted solution prior to administration. Do not use if there is discolouration of the reconstituted solution or if particulate matter is present. Discard any solution that is left in the vial after you give

yourself the injection.

Inject PegIntron once each week on the same day. Injecting it at the same time of day each week will help you not to forget to take it.

Use PegIntron exactly as prescribed by your doctor. Do not exceed the recommended dosage, and take it for as long as prescribed.

If you use more PegIntron than you should:
Tell your doctor or healthcare professional as soon as possible.

If you forget to take PegIntron:
Take the dose as soon as you remember, then continue your treatment as usual.
Do not take a double dose to make up for forgotten individual doses. Contact your doctor or pharmacist if needed.

4. POSSIBLE SIDE EFFECTS

Like all medicines, PegIntron can have side effects. Although not all of these side effects may occur, they may need medical attention if they do.

Check with your doctor immediately if any of the following side effects occur: chest pain; changes in the way your heart beats; breathing problems, (including shortness of breath), confusion; feeling depressed, wanting to harm yourself, hallucinations, numbness or tingling feeling; dizziness, convulsion ("fit"); trouble sleeping, thinking or concentrating; difficulty remaining alert, severe stomach pain or cramps; blood or clots in stool (or black, tarry stool); fever or chills beginning after a few weeks of treatment, pain in your lower back or side; difficulty or inability to pass urine, painful or inflamed muscles (sometimes severe); problems with your eyes or your eyesight or hearing; severe or painful reddening of your skin or mucous membrane, severe bleeding from your nose. Your doctor will test your blood to ensure that your white blood cell (cells that fight infection) and red blood cell (cells that carry oxygen) counts, platelets (blood clotting cells) and other laboratory values are at acceptable levels.

Some people get depressed when taking PegIntron alone or in combination treatment with ribavirin, and in some cases people had suicidal thoughts or aggressive behaviour. Some patients have actually committed suicide. Be sure to seek emergency care if you notice that you are becoming depressed or have suicidal thoughts or change in your behaviour. You may want to consider asking a family member or close friend to help you stay alert to signs of depression or changes in your behaviour.

The most common side effects with the combination of PegIntron and ribavirin capsules are irritation or redness (and rarely, skin damage) at the site of injection, headache, tired feeling, shaking chills, fever, flu-like symptoms, weakness, loss of weight, nausea, loss of appetite, diarrhoea or loose stools, stomach pain, vomiting, muscle aches, pain in joints and muscles, feeling depressed, irritability, trouble falling asleep or staying asleep, feeling anxious or nervous, difficulty concentrating, mood swings, hair loss, itching, dry skin, sore throat, coughing, difficult breathing, dizziness, virus infection, rash, and dry mouth.

Other common side effects that may occur with combination treatment are increased sweating, chest pain, pain on the right side around your ribs, numbness, pain or tingling feeling, change in thyroid gland activity (which may make you feel tired or, less commonly, energetic), stomach upset, rapid heart rate, agitation, nervousness, difficult or irregular menstrual period.

Less common are pain at the place of injection, flushing, low or high blood pressure, dry or teary eyes, redness of skin or skin disorders, psoriasis, hives, nail disorder, feeling unwell, feeling faint, poor coordination, confusion, increased or decreased sensitivity to touch, tense muscles, arthritis, bruising, loss of interest in activities including sex, sexual problem, unusual dreams, shaky hands, vertigo (spinning feeling), increased appetite, heartburn, intestinal gas (flatus), constipation, hemorrhoids, red or bleeding

gums, redness or sores in mouth, change in taste, changes in hearing or ringing in ears, thirst, aggressive or changed behaviour, feeling sleepy, cold sores, fungal or bacterial infections, irritation of prostate gland, increased need to pass urine, ear or respiratory infections, sinusitis, stuffy or runny nose, abnormal hair texture, sensitivity to sunlight, migraine headache, eye pain or infection, blurred vision, puffy face, puffy hands or feet, enlarged liver, problem affecting ovary or vagina, pain in breast, difficulty in speaking, diabetes and swollen glands.

Very rarely sarcoidosis (a disease characterised by persistent fever, weight loss, joint pain and swelling, skin lesions and swollen glands) has been reported. Loss of consciousness has occurred very rarely with alpha interferons, mostly in elderly patients treated at high doses. Cases of stroke (cerebrovascular events) have been reported. Check with your doctor immediately if you have any of these symptoms or any other symptoms that are troubling.

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Do not use PegIntron if you notice discolouration of the powder.

6. FURTHER INFORMATION

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- a short needle (for example 0.3 × 13 mm [30 gauge 0.5 inch]) for the subcutaneous injection;
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Remove the protective cap from the PegIntron vial. Clean the rubber top of the vial with a cleansing swab. You can save the swab to clean the skin area where you will inject the dose. Remove the syringe from the wrapping. Do not touch the tip of the syringe. Take the long needle and place it firmly on to the tip of the syringe. Remove the needle guard without touching the needle and keep the syringe with the needle in your hand. Tap the top of the ampoule of solvent gently to make sure that all the liquid is at the bottom of the ampoule. Break off the top of the ampoule of solvent. Insert the needle in the ampoule of solvent and withdraw the total amount of solvent.

When the total amount of solvent is combined with the full amount of PegIntron powder, the solution will be at the correct concentration to measure your dose (i.e., the labelled amount is contained in 0.5 ml).

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Inject the solvent **SLOWLY**, aiming the stream of liquid at the glass wall of the vial. It is best not to aim the stream directly at the white solid or powder, or to inject the liquid quickly, as this causes a greater amount of bubbles. The solution may appear cloudy or bubbly for a few minutes. This is to be expected and is not cause for concern.

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Measuring the dose of PegIntron from the reconstituted powder for injection
Turn the vial and the syringe upside down in one hand. Be sure the tip of needle is in the PegIntron reconstituted solution. Your other hand will be free to move the plunger. Pull back on the plunger

slowly to draw just more than the dose prescribed by your doctor into the syringe.
Hold the syringe with the needle in the vial pointing up, remove the syringe from the long needle leaving the needle in the vial and without touching the tip of the syringe. Take the short needle and place it firmly on to the tip of the syringe. Remove the needle guard from the syringe needle and check for air bubbles in the syringe. If you see any bubbles, pull the plunger slightly back; tap the syringe gently, with the needle pointing upwards, until the bubbles disappear. Push up the plunger slowly back to the correct dose. Replace the needle guard and place the syringe with the needle on a flat surface.

Be sure the solution is at room temperature up to 25°C. If the solution is cold, warm the syringe between your palms. Inspect visually the reconstituted solution prior to administration: do not use if discolouration or particulate matter is present. You are now ready to inject the dose.

Injecting the solution
Select the injection site. The best sites for injection are tissues with a layer of fat between skin and muscle: thigh, outer surface of the upper arm (you may need the assistance of another person to use this site), abdomen (except the navel or waistline). If you are exceptionally thin, use only the thigh or outer surface of the arm for injection.
Change your injection site each time.

Cleanse and disinfect the skin where the injection is to be made. Wait for the area to dry. Remove the needle guard. With one hand, pinch a fold of loose skin. With your other hand, hold the syringe as you would a pencil. Insert the needle into the pinched skin at an angle of approximately 45°. After the needle is in, remove the hand used to pinch the skin and use it to hold the syringe barrel. Pull back the plunger very slightly with one hand. If blood comes into the syringe, the needle has entered a blood vessel. Do not inject into this site; withdraw the needle and repeat the procedure. Inject the solution by pushing the plunger all the way down gently.
Pull the needle straight out of the skin. Press the injection site with a small bandage or sterile gauze if necessary for several seconds. Do not massage the injection site. If there is bleeding, cover with an adhesive bandage.
The vial, ampoule and injection materials intended for single use must be discarded. Dispose of the syringe and needles safely in a closed container.

PACKAGE LEAFLET

Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

In this leaflet:

PegIntron 150 micrograms powder and solvent for solution for injection
peginterferon alfa-2b (conjugation of recombinant interferon alfa-2b with monomethoxy polyethylene glycol)

- The active substance is peginterferon alfa-2b, 150 micrograms/0.5 ml.
- The other ingredients are:
  Powder: disodium phosphate, anhydrous; sodium dihydrogen phosphate dihydrate, sucrose and polysorbate 80;
  Solvent: water for injections 0.7 ml/ampoule.

Marketing Authorisation Holder: SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

Manufacturer: SP (Brinny) Company, Innishannon, County Cork, Ireland

1. WHAT PEGINTRON IS AND WHAT IT IS USED FOR

The pharmaceutical form is: powder and solvent for solution for injection.
The white powder is contained in a 2 ml glass vial and the clear and colourless solvent is presented in a 2 ml glass ampoule.

PegIntron 150 micrograms is available in different pack sizes:
- 1 vial of powder for solution for injection and 1 ampoule of solvent for parenteral use;
- 1 vial of powder for solution for injection, 1 ampoule of solvent for parenteral use, 1 injection syringe, 2 injection needles and 1 cleansing swab;
- 4 vials of powder for solution for injection and 4 ampoules of solvent for parenteral use;
- 4 vials of powder for solution for injection, 4 ampoules of solvent for parenteral use, 4 injection syringes, 8 injection needles and 4 cleansing swabs;
- 6 vials of powder for solution for injection and 6 ampoules of solvent for parenteral use;
- 12 vials of powder for solution for injection, 12 ampoules of solvent for parenteral use, 12 injection syringes, 24 injection needles and 12 cleansing swabs.

Not all pack sizes may be marketed.

Interferons modify the response of the body's immune system to help fight infections and severe diseases. PegIntron, which contains an interferon, is used for the treatment of chronic hepatitis C, a viral infection of the liver.

PegIntron is best used for this treatment in combination with ribavirin.

PegIntron is used alone in case of intolerance or contraindication to ribavirin.

2. BEFORE YOU USE PEGINTRON

PegIntron is not recommended for use in patients under the age of 18 years.

Do not use PegIntron:
- If you are hypersensitive (allergic) to peginterferon alfa-2b or any of the other ingredients of PegIntron.
- If you are hypersensitive (allergic) to any interferon.
- If you are pregnant or breast feeding.
- If you have had severe heart problems, or if you have heart disease that has not been well controlled during the past 6 months.
- If you have severe medical conditions that leave you very weak, including severe kidney disease.
- If you have autoimmune hepatitis or any other problem with your immune system; if you are taking medicine that suppresses your immune system (your immune system protects you against infection and some diseases).
- If you have advanced, uncontrolled liver disease (other than hepatitis C).
- If you have thyroid disease that is not well controlled with medicines.
- If you have a condition that causes convulsions (seizures, or "fits").

Take special care with PegIntron:
- If you develop symptoms of a severe allergic reaction (such as difficulty in breathing, wheezing, or hives) while on this medication, seek medical help immediately.
- If you ever had a heart attack or a heart problem.
- If you have ever been treated for depression or any other nervous or mental disorder.
- If you have had a problem with your liver (other than hepatitis C).
- If you develop symptoms associated with a cold or other respiratory infection, such as fever, cough, or any difficulty in breathing, tell your doctor.
- If you are diabetic, your doctor may ask you to have an eye examination.
- If you have had any serious illness affecting your breathing or your blood.
- If you have psoriasis, it may become worse while you are using PegIntron.
- If you are planning to become pregnant, discuss this with your doctor before starting to use PegIntron.
- If you are also being treated for HIV, please see **Using other medicines**.
- If you have had a severe nervous or mental disorder.
- If you have received an organ transplant, either kidney or liver, interferon treatment may increase the risk of rejection. Be sure to discuss this with your doctor.

While being treated with PegIntron
Your doctor may want you to drink extra fluids to help prevent low blood pressure.

Pregnancy
Ask your doctor or pharmacist for advice before taking any medicine. Do not use PegIntron during pregnancy. The effect on human pregnancy is not known.

Breast-feeding
Ask your doctor or pharmacist for advice before taking any medicine. It is not known whether this product is present in human milk. Therefore, do not breast-feed an infant if you are taking PegIntron.

Driving and using machines:
Do not drive or operate any tools or machines if you feel tired, sleepy or confused while taking PegIntron.

Using other medicines:

Please inform your doctor or pharmacist if you are taking or have recently taken any other medicines, even those not prescribed.

Important information about some of the ingredients of PegIntron:
This medicinal product contains less than 1 mmol sodium (23 mg) per 0.7 ml, i.e., essentially "sodium-free".

Patients who also have HIV infection:
Lactic acidosis and worsening liver function are side effects associated with Highly Active Anti-Retroviral Therapy (HAART), an HIV treatment. If you are receiving HAART, the addition of PegIntron and ribavirin may increase your risk of lactic acidosis and of liver failure. Your doctor will monitor you for signs and symptoms of these conditions. (Please be sure to read the ribavirin Patient Leaflet also).

3. HOW TO USE PEGINTRON

Your doctor has prescribed PegIntron specifically for you and your current condition; do not share this medicine with anyone else.

Your doctor has determined your dose of PegIntron based on your weight. If necessary, the dose may be changed during treatment.

Combination treatment
PegIntron, when given with ribavirin capsules, is usually given at a dose of 1.5 microgram/kg once a week.

Ribavirin capsules are taken every day, morning and evening. The number of ribavirin capsules you take depends on your weight.
- If you weigh less than 65 kg, take 2 capsules in the morning and 2 in the evening (total of 800 mg each day).
- If you weigh between 65 and 85 kg, take 2 capsules in the morning and 3 in the evening (total of 1,000 mg each day).
- If you weigh more than 85 kg, take 3 capsules in the morning and 3 in the evening (total 1,200 mg each day).

The combination treatment is continued for at least 6 months, and sometimes for one year.

PegIntron alone:
PegIntron, when given alone, is usually given at a dose of 0.5 or 1.0 microgram/kg once a week, for at least 6 months, and possibly for 1 year.

All patients:
If you are injecting PegIntron yourself, please be sure that the dose that has been prescribed for you is clearly provided on the package of medicine you receive.

If you have the impression that the effect of PegIntron is too strong or too weak, talk to your doctor or pharmacist.

PegIntron is intended for subcutaneous use. This means that it is injected through a short injection needle into the fatty tissue just under your skin. If you are injecting this medicine yourself, you will be instructed how to prepare and give the injection. Detailed instructions for subcutaneous administration are provided with this leaflet (see How to self-inject PegIntron at the end of the package leaflet).

Prepare the dose just before you intend to inject it and use it immediately. Look carefully at the reconstituted solution prior to administration. Do not use if there is discolouration of the reconstituted solution or if particulate matter is present. Discard any solution that is left in the vial after you give

yourself the injection.

Inject PegIntron once each week on the same day. Injecting it at the same time of day each week will help you not to forget to take it.

Use PegIntron exactly as prescribed by your doctor. Do not exceed the recommended dosage, and take it for as long as prescribed.

If you use more PegIntron than you should:
Tell your doctor or healthcare professional as soon as possible.

If you forget to take PegIntron:
Take the dose as soon as you remember, then continue your treatment as usual.
Do not take a double dose to make up for forgotten individual doses. Contact your doctor or pharmacist if needed.

4. POSSIBLE SIDE EFFECTS

Like all medicines, PegIntron can have side effects. Although not all of these side effects may occur, they may need medical attention if they do.

Check with your doctor immediately if any of the following side effects occur: chest pain; changes in the way your heart beats; breathing problems, (including shortness of breath), confusion; feeling depressed, wanting to harm yourself, hallucinations, numbness or tingling feeling; dizziness, convulsion ("fit"); trouble sleeping, thinking or concentrating; difficulty remaining alert, severe stomach pain or cramps; blood or clots in stool (or black, tarry stool); fever or chills beginning after a few weeks of treatment, pain in your lower back or side; difficulty or inability to pass urine, painful or inflamed muscles (sometimes severe); problems with your eyes or your eyesight or hearing; severe or painful reddening of your skin or mucous membrane, severe bleeding from your nose. Your doctor will test your blood to ensure that your white blood cell (cells that fight infection) and red blood cell (cells that carry oxygen) counts, platelets (blood clotting cells) and other laboratory values are at acceptable levels.

Some people get depressed when taking PegIntron alone or in combination treatment with ribavirin, and in some cases people had suicidal thoughts or aggressive behaviour. Some patients have actually committed suicide. Be sure to seek emergency care if you notice that you are becoming depressed or have suicidal thoughts or change in your behaviour. You may want to consider asking a family member or close friend to help you stay alert to signs of depression or changes in your behaviour.

The most common side effects with the combination of PegIntron and ribavirin capsules are irritation or redness (and rarely, skin damage) at the site of injection, headache, tired feeling, shaking chills, fever, flu-like symptoms, weakness, loss of weight, nausea, loss of appetite, diarrhoea or loose stools, stomach pain, vomiting, muscle aches, pain in joints and muscles, feeling depressed, irritability, trouble falling asleep or staying asleep, feeling anxious or nervous, difficulty concentrating, mood swings, hair loss, itching, dry skin, sore throat, coughing, difficult breathing, dizziness, virus infection, rash, and dry mouth.

Other common side effects that may occur with combination treatment are increased sweating, chest pain, pain on the right side around your ribs, numbness, pain or tingling feeling, change in thyroid gland activity (which may make you feel tired or, less commonly, energetic), stomach upset, rapid heart rate, agitation, nervousness, difficult or irregular menstrual period.

Less common are pain at the place of injection, flushing, low or high blood pressure, dry or teary eyes, redness of skin or skin disorders, psoriasis, hives, nail disorder, feeling unwell, feeling faint, poor coordination, confusion, increased or decreased sensitivity to touch, tense muscles, arthritis, bruising, loss of interest in activities including sex, sexual problem, unusual dreams, shaky hands, vertigo (spinning feeling), increased appetite, heartburn, intestinal gas (flatus), constipation, hemorrhoids, red or bleeding

gums, redness or sores in mouth, change in taste, changes in hearing or ringing in ears, thirst, aggressive or changed behaviour, feeling sleepy, cold sores, fungal or bacterial infections, irritation of prostate gland, increased need to pass urine, ear or respiratory infections, sinusitis, stuffy or runny nose, abnormal hair texture, sensitivity to sunlight, migraine headache, eye pain or infection, blurred vision, puffy face, puffy hands or feet, enlarged liver, problem affecting ovary or vagina, pain in breast, difficulty in speaking, diabetes and swollen glands.

Very rarely sarcoidosis (a disease characterised by persistent fever, weight loss, joint pain and swelling, skin lesions and swollen glands) has been reported. Loss of consciousness has occurred very rarely with alpha interferons, mostly in elderly patients treated at high doses. Cases of stroke (cerebrovascular events) have been reported. Check with your doctor immediately if you have any of these symptoms or any other symptoms that are troubling.

Very rarely, PegIntron alone or in combination with ribavirin may cause aplastic anaemia.

When PegIntron is used alone, some of these effects are less likely to occur, and some have not occurred at all.

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

5. STORING PEGINTRON

Keep out of the reach and sight of children.

Store in a refrigerator (2°C - 8°C).

Do not use after the expiry date stated on the carton.
After reconstitution, use the reconstituted solution immediately or within 24 hours when stored at 2°C - 8°C (in a refrigerator).

Do not use PegIntron if you notice discolouration of the powder.

6. FURTHER INFORMATION

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

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HOW TO SELF-INJECT PEGINTRON?

The following instructions explain how to inject PegIntron yourself. Please read the instructions carefully and follow them step by step. Your doctor or his/her assistant will instruct you how to self-inject PegIntron. Do not attempt to inject yourself unless you are sure you understand the procedure and requirement of self-injection.

Preparation
Collect necessary items before you begin:
- a vial of PegIntron powder for injection;
- an ampoule of solvent for PegIntron (water for injections);
- a 1 ml syringe;
- a long needle (for example 0.8 × 40 mm [21 gauge 1.5 inch]) to be used to add water for injections to the PegIntron powder vial;
- a short needle (for example 0.3 × 13 mm [30 gauge 0.5 inch]) for the subcutaneous injection;
- a cleansing swab.

Wash your hands carefully.

Reconstituting PegIntron powder for injection
Before reconstitution, PegIntron may appear either as a white, tablet-shaped solid that is whole or in pieces, or as a white powder.
Remove the protective cap from the PegIntron vial. Clean the rubber top of the vial with a cleansing swab. You can save the swab to clean the skin area where you will inject the dose. Remove the syringe from the wrapping. Do not touch the tip of the syringe. Take the long needle and place it firmly on to the tip of the syringe. Remove the needle guard without touching the needle and keep the syringe with the needle in your hand. Tap the top of the ampoule of solvent gently to make sure that all the liquid is at the bottom of the ampoule. Break off the top of the ampoule of solvent. Insert the needle in the ampoule of solvent and withdraw the total amount of solvent.

When the total amount of solvent is combined with the full amount of PegIntron powder, the solution will be at the correct concentration to measure your dose (i.e., the labelled amount is contained in 0.5 ml).

A small volume is lost during preparation of PegIntron for injection and when the dose is measured and injected. Therefore, each vial contains an excess amount of solvent and PegIntron powder to ensure delivery of the labelled dose in 0.5 ml of PegIntron, solution for injection.

To prepare the PegIntron solution, insert the needle through the rubber top of the PegIntron vial and gently place the needle tip against the glass wall of the vial without touching the cleaned top of the vial with your hands.
Inject the solvent **SLOWLY**, aiming the stream of liquid at the glass wall of the vial. It is best not to aim the stream directly at the white solid or powder, or to inject the liquid quickly, as this causes a greater amount of bubbles. The solution may appear cloudy or bubbly for a few minutes. This is to be expected and is not cause for concern.

To dissolve the entire contents, swirl the PegIntron vial with a gentle rotary motion leaving the needle and attached syringe in the vial. **Do not shake**, but gently turn the vial upside down until any powder at the top of the vial is dissolved. The contents should now be completely dissolved. Stand the vial upright and let any bubbles present in the solution rise to the top of the solution. Once the solution has settled and all bubbles have risen to the top of the solution, you should have a clear solution with a small ring of tiny bubbles around the top. Now you can withdraw your dose from the vial. Use this solution immediately. If it cannot be used immediately, the solution may be refrigerated for up to 24 hours.

Measuring the dose of PegIntron from the reconstituted powder for injection
Turn the vial and the syringe upside down in one hand. Be sure the tip of needle is in the PegIntron reconstituted solution. Your other hand will be free to move the plunger. Pull back on the plunger

slowly to draw just more than the dose prescribed by your doctor into the syringe.
Hold the syringe with the needle in the vial pointing up, remove the syringe from the long needle leaving the needle in the vial and without touching the tip of the syringe. Take the short needle and place it firmly on to the tip of the syringe. Remove the needle guard from the syringe needle and check for air bubbles in the syringe. If you see any bubbles, pull the plunger slightly back; tap the syringe gently, with the needle pointing upwards, until the bubbles disappear. Push up the plunger slowly back to the correct dose. Replace the needle guard and place the syringe with the needle on a flat surface.

Be sure the solution is at room temperature up to 25°C. If the solution is cold, warm the syringe between your palms. Inspect visually the reconstituted solution prior to administration: do not use if discolouration or particulate matter is present. You are now ready to inject the dose.

Injecting the solution
Select the injection site. The best sites for injection are tissues with a layer of fat between skin and muscle: thigh, outer surface of the upper arm (you may need the assistance of another person to use this site), abdomen (except the navel or waistline). If you are exceptionally thin, use only the thigh or outer surface of the arm for injection.
Change your injection site each time.

Cleanse and disinfect the skin where the injection is to be made. Wait for the area to dry. Remove the needle guard. With one hand, pinch a fold of loose skin. With your other hand, hold the syringe as you would a pencil. Insert the needle into the pinched skin at an angle of approximately 45°. After the needle is in, remove the hand used to pinch the skin and use it to hold the syringe barrel. Pull back the plunger very slightly with one hand. If blood comes into the syringe, the needle has entered a blood vessel. Do not inject into this site; withdraw the needle and repeat the procedure. Inject the solution by pushing the plunger all the way down gently.
Pull the needle straight out of the skin. Press the injection site with a small bandage or sterile gauze if necessary for several seconds. Do not massage the injection site. If there is bleeding, cover with an adhesive bandage.
The vial, ampoule and injection materials intended for single use must be discarded. Dispose of the syringe and needles safely in a closed container.

PACKAGE LEAFLET

Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

In this leaflet:

PegIntron 50 micrograms powder and solvent for solution for injection in pre-filled pen
Peginterferon alfa-2b (conjugation of recombinant interferon alfa-2b with monomethoxy polyethylene glycol)

- The active substance is peginterferon alfa-2b, 50 micrograms/0.5 ml.
- The other ingredients are:
  Powder: disodium phosphate, anhydrous; sodium dihydrogen phosphate dihydrate, sucrose and polysorbate 80;
  Solvent: water for injections

Marketing Authorisation Holder: SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

Manufacturer: SP (Brinny) Company, Innishannon, County Cork, Ireland

1. WHAT PEGINTRON IS AND WHAT IT IS USED FOR

The pharmaceutical form is: powder and solvent for solution for injection.
The white powder and the clear and colourless solvent are both contained in a two-chamber glass cartridge assembled into a single use pre-filled pen.

PegIntron 50 micrograms is available in different pack sizes:
- 1 pen containing powder and solvent for solution for injection, 1 injection needle and 2 cleansing swabs;
- 4 pens containing powder and solvent for solution for injection, 4 injection needles and 8 cleansing swabs;
- 6 pens containing powder and solvent for solution for injection, 6 injection needles and 12 cleansing swabs;
- 12 pens containing powder and solvent for solution for injection, 12 injection needles and 24 cleansing swabs.

Not all pack sizes may be marketed.

Interferons modify the response of the body's immune system to help fight infections and severe diseases. PegIntron, which contains an interferon, is used for the treatment of chronic hepatitis C, a viral infection of the liver.

PegIntron is best used for this treatment in combination with ribavirin.

PegIntron is used alone in case of intolerance or contraindication to ribavirin.

2. BEFORE YOU USE PEGINTRON

PegIntron is not recommended for use in patients under the age of 18 years.

Do not use PegIntron:
- If you are hypersensitive (allergic) to peginterferon alfa-2b or any of the other ingredients of PegIntron.
- If you are hypersensitive (allergic) to any interferon.
- If you are pregnant or breast feeding.
- If you have had severe heart problems, or if you have heart disease that has not been well controlled during the past 6 months.
- If you have severe medical conditions that leave you very weak, including severe kidney disease.
- If you have autoimmune hepatitis or any other problem with your immune system; if you are taking medicine that suppresses your immune system (your immune system protects you against infection and some diseases).
- If you have advanced, uncontrolled liver disease (other than hepatitis C).
- If you have thyroid disease that is not well controlled with medicines.
- If you have a condition that causes convulsions (seizures, or "fits").

Take special care with PegIntron:
- If you develop symptoms of a severe allergic reaction (such as difficulty in breathing, wheezing, or hives) while on this medication, seek medical help immediately.
- If you ever had a heart attack or a heart problem.
- If you have ever been treated for depression or any other nervous or mental disorder.
- If you have had a problem with your liver (other than hepatitis C).
- If you develop symptoms associated with a cold or other respiratory infection, such as fever, cough, or any difficulty in breathing, tell your doctor.
- If you are diabetic, your doctor may ask you to have an eye examination.
- If you have had any serious illness affecting your breathing or your blood.
- If you have psoriasis, it may become worse while you are using PegIntron.
- If you are planning to become pregnant, discuss this with your doctor before starting to use PegIntron.
- If you are also being treated for HIV, please see **Using other medicines**.
- If you have had a severe nervous or mental disorder.
- If you have received an organ transplant, either kidney or liver, interferon treatment may increase the risk of rejection. Be sure to discuss this with your doctor.

While being treated with PegIntron
Your doctor may want you to drink extra fluids to help prevent low blood pressure.

Pregnancy
Ask your doctor or pharmacist for advice before taking any medicine. Do not use PegIntron during pregnancy. The effect on human pregnancy is not known.

Breast-feeding
Ask your doctor or pharmacist for advice before taking any medicine. It is not known whether this product is present in human milk. Therefore, do not breast-feed an infant if you are taking PegIntron.

Driving and using machines:
Do not drive or operate any tools or machines if you feel tired, sleepy or confused while taking PegIntron.

Using other medicines:
Please inform your doctor or pharmacist if you are taking or have recently taken any other medicines, even those not prescribed.

Important information about some of the ingredients of PegIntron:
This medicinal product contains less than 1 mmol sodium (23 mg) per 0.7 ml, i.e., essentially "sodium-free".

Patients who also have HIV infection:
Lactic acidosis and worsening liver function are side effects associated with Highly Active Anti-Retroviral Therapy (HAART), an HIV treatment. If you are receiving HAART, the addition of PegIntron and ribavirin may increase your risk of lactic acidosis and of liver failure. Your doctor will monitor you for signs and symptoms of these conditions. (Please be sure to read the ribavirin Patient Leaflet also).

3. HOW TO USE PEGINTRON

Your doctor has prescribed PegIntron specifically for you and your current condition; do not share this medicine with anyone else.

Your doctor has determined your dose of PegIntron based on your weight. If necessary, the dose may be changed during treatment.

Combination treatment
PegIntron, when given with ribavirin capsules, is usually given at a dose of 1.5 microgram/kg once a week.

Ribavirin capsules are taken every day, morning and evening. The number of ribavirin capsules you take depends on your weight.
- If you weigh less than 65 kg, take 2 capsules in the morning and 2 in the evening (total of 800 mg each day).
- If you weigh between 65 and 85 kg, take 2 capsules in the morning and 3 in the evening (total of 1,000 mg each day).
- If you weigh more than 85 kg, take 3 capsules in the morning and 3 in the evening (total 1,200 mg each day).

The combination treatment is continued for at least 6 months, and sometimes for one year.

PegIntron alone:
PegIntron, when given alone, is usually given at a dose of 0.5 or 1.0 microgram/kg once a week, for at least 6 months, and possibly for 1 year.

All patients:
If you are injecting PegIntron yourself, please be sure that the dose that has been prescribed for you is clearly provided on the package of medicine you receive.

If you have the impression that the effect of PegIntron is too strong or too weak, talk to your doctor or pharmacist.

PegIntron is intended for subcutaneous use. This means that it is injected through a short injection needle into the fatty tissue just under your skin. If you are injecting this medicine yourself, you will be instructed how to prepare and give the injection. Detailed instructions for subcutaneous administration are provided with this leaflet (see How to use the PegIntron pre-filled pen).

Prepare the dose just before you intend to inject it and use it immediately. Look carefully at the reconstituted solution prior to administration. Do not use if there is discolouration of the reconstituted solution or if particulate matter is present. PegIntron is intended for single use only. Thus, after you give yourself the injection, discard the PegIntron pre-filled pen with any solution that is left in it.

Inject PegIntron once each week on the same day. Injecting it at the same time of day each week will help you not to forget to take it.

Use PegIntron exactly as prescribed by your doctor. Do not exceed the recommended dosage, and take it for as long as prescribed.

If you use more PegIntron than you should:
Tell your doctor or healthcare professional as soon as possible.

If you forget to take PegIntron:
Take the dose as soon as you remember, then continue your treatment as usual.
Do not take a double dose to make up for forgotten individual doses. Contact your doctor or pharmacist if needed.

4. POSSIBLE SIDE EFFECTS

Like all medicines, PegIntron can have side effects. Although not all of these side effects may occur, they may need medical attention if they do.

Check with your doctor immediately if any of the following side effects occur: chest pain; changes in the way your heart beats; breathing problems, (including shortness of breath), confusion; feeling depressed, wanting to harm yourself, hallucinations, numbness or tingling feeling; dizziness, convulsion ("fit"); trouble sleeping, thinking or concentrating; difficulty remaining alert, severe stomach pain or cramps; blood or clots in stool (or black, tarry stool); fever or chills beginning after a few weeks of treatment, pain in your lower back or side; difficulty or inability to pass urine, painful or inflamed muscles (sometimes severe); problems with your eyes or your eyesight or hearing; severe or painful reddening of your skin or mucous membrane, severe bleeding from your nose. Your doctor will test your blood to ensure that your white blood cell (cells that fight infection) and red blood cell (cells that carry oxygen) counts, platelets (blood clotting cells) and other laboratory values are at acceptable levels.

Some people get depressed when taking PegIntron alone or in combination treatment with ribavirin, and in some cases people had suicidal thoughts or aggressive behaviour. Some patients have actually committed suicide. Be sure to seek emergency care if you notice that you are becoming depressed or have suicidal thoughts or change in your behaviour. You may want to consider asking a family member or close friend to help you stay alert to signs of depression or changes in your behaviour.

The most common side effects with the combination of PegIntron and ribavirin capsules are irritation or redness (and rarely, skin damage) at the site of injection, headache, tired feeling, shaking chills, fever, flu-like symptoms, weakness, loss of weight, nausea, loss of appetite, diarrhoea or loose stools, stomach pain, vomiting, muscle aches, pain in joints and muscles, feeling depressed, irritability, trouble falling asleep or staying asleep, feeling anxious or nervous, difficulty concentrating, mood swings, hair loss, itching, dry skin, sore throat, coughing, difficult breathing, dizziness, virus infection, rash, and dry mouth.

Other common side effects that may occur with combination treatment are increased sweating, chest pain, pain on the right side around your ribs, numbness, pain or tingling feeling, change in thyroid gland activity (which may make you feel tired or, less commonly, energetic), stomach upset, rapid heart rate, agitation, nervousness, difficult or irregular menstrual period.

Less common are pain at the place of injection, flushing, low or high blood pressure, dry or teary eyes, redness of skin or skin disorder, psoriasis, hives, nail disorder, feeling unwell, feeling faint, poor coordination, confusion, increased or decreased sensitivity to touch, tense muscles, arthritis, bruising, loss of interest in activities including sex, sexual problem, unusual dreams, shaky hands, vertigo (spinning feeling), increased appetite, heartburn, intestinal gas (flatus), constipation, hemorrhoids, red or bleeding gums, redness or sores in mouth, change in taste, changes in hearing or ringing in ears, thirst, aggressive or changed behaviour, feeling sleepy, cold sores, fungal or bacterial infections, irritation of prostate gland,

increased need to pass urine, ear or respiratory infections, sinusitis, stuffy or runny nose, abnormal hair texture, sensitivity to sunlight, migraine headache, eye pain or infection, blurred vision, puffy face, puffy hands or feet, enlarged liver, problem affecting ovary or vagina, pain in breast, difficulty in speaking, diabetes and swollen glands.

Very rarely sarcoidosis (a disease characterised by persistent fever, weight loss, joint pain and swelling, skin lesions and swollen glands) has been reported. Loss of consciousness has occurred very rarely with alpha interferons, mostly in elderly patients treated at high doses. Cases of stroke (cerebrovascular events) have been reported. Check with your doctor immediately if you have any of these symptoms or any other symptoms that are troubling.

Very rarely, PegIntron alone or in combination with ribavirin may cause aplastic anaemia.

When PegIntron is used alone, some of these effects are less likely to occur, and some have not occurred at all.

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

5. STORING PEGINTRON

Keep out of the reach and sight of children.

Store in a refrigerator (2°C - 8°C). Do not freeze.

Do not use after the expiry date stated on the carton.
After reconstitution, use the reconstituted solution immediately or within 24 hours when stored at 2°C - 8°C (in a refrigerator).

Do not use PegIntron if you notice discolouration of the reconstituted solution.

6. FURTHER INFORMATION

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

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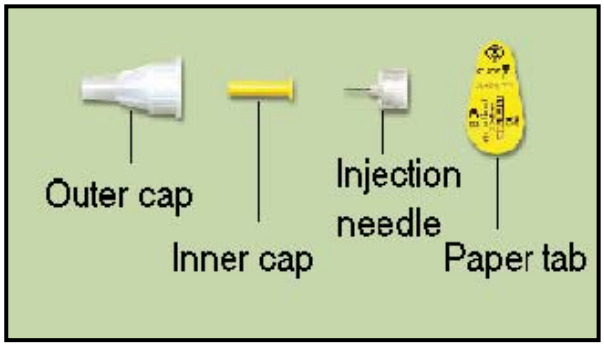
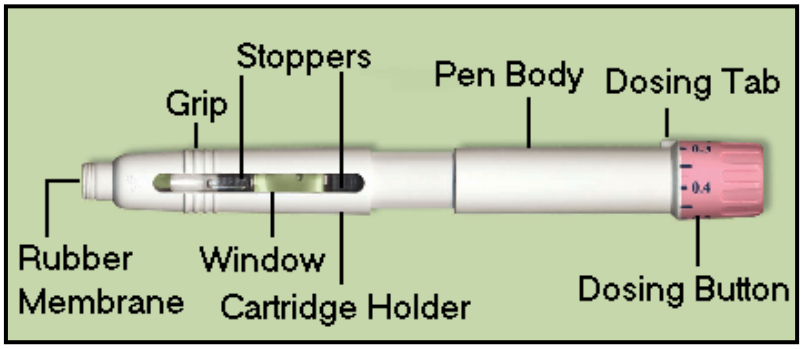
This leaflet was last approved on

ANNEX TO THE PACKAGE LEAFLET

How to use the PegIntron pre-filled pen





The following instructions explain how to inject yourself with the single use PegIntron pre-filled pen. **Please read the instructions carefully and completely before attempting to use the pen and follow them step by step.** Your doctor or his/her assistant will instruct you on how to self-inject with the PegIntron pre-filled pen. Do not attempt to inject yourself unless you are sure you understand the procedure and requirements for self-injection.

The PegIntron pre-filled pen is intended for use by one person only and must not be shared. Use the injection needle and cleansing swabs provided in the packaging only for the PegIntron pre-filled pen. Be sure the solution is at room temperature at the time of injection. Your doctor will have told you what dose you require for your therapy.

Note: The colour of the dosing button is different for each strength of the PegIntron pre-filled pen.

Step 1: Mixing

It is important that you keep the PegIntron pre-filled pen upright (as shown in figure 1) during mixing, unless otherwise instructed.

- Take the PegIntron pre-filled pen out of the refrigerator. Allow the medicine to come to room temperature.

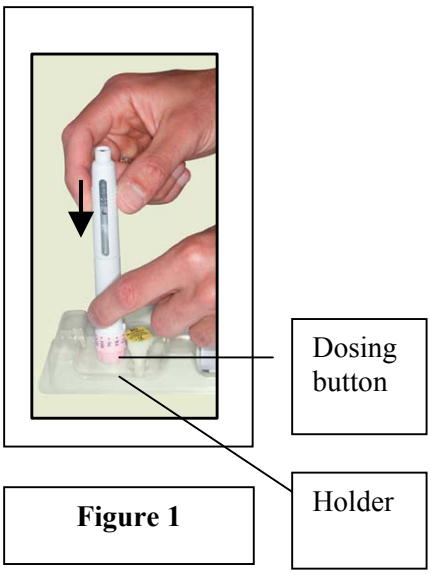
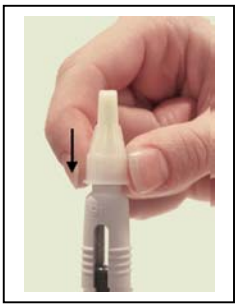


Figure 1

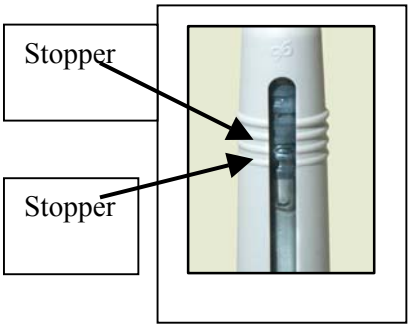
- Wash your hands with soap and water.
- **Place the PegIntron pre-filled pen upright** in the holder of the tray provided in the pack (the dosing button will be on the **bottom**).
- You may want to hold the pre-filled pen using the grip. To mix the powder and the liquid, press the two halves together firmly by pressing down until you hear the pre-filled pen click. The two stoppers should come together.
- Wait for several seconds until the powder is completely dissolved.
- **Gently turn the PegIntron pre-filled pen upside down twice. To avoid excessive foaming, do not shake.**
- Maintaining the PegIntron pre-filled pen upright, check the mixed PegIntron solution through the window. If there is still foam, wait until it settles. The solution should be clear and colourless. **Do not use the pen if the solution is discoloured or contains any particles.**



- Keeping the PegIntron pre-filled pen upright in the holder provided in the packaging, disinfect the rubber membrane of the PegIntron pre-filled pen with one cleansing swab.
- Take the injection needle provided in the tray and remove its protective paper tab.
- **Maintaining the PegIntron pre-filled pen upright in the holder,** gently push the injection needle onto the pre-filled pen and **screw it securely in place**.

Figure 2

- **Keep the PegIntron pre-filled pen pointed up**.
- **Do not take off the outer needle cap at this point.**
- You may see some liquid trickle out from under the cap, as the air has been expelled out of the pen.
- Wait about 5 seconds for this process to finish.



- **Check through the window to be sure that the two stoppers are together. If they are not together, do not use this pen because you may not be able to dial your dose.**

Figure 3

Step 2: Setting the dose

- Remove the PegIntron pre-filled pen from the holder.
- Holding the PegIntron pre-filled pen firmly, pull the dosing button out as far as it will go, until you see a **dark ring** on the pen. The dosing button should be easy to pull out without excessive force being required.

Note: Do not push the dosing button back in at this time. You will push it in when you are ready to self-inject the PegIntron.

Figure 4

Figure 5

- Turn the dosing button until your prescribed dose is aligned with the dosing tab. The button should turn easily without excessive force being required.

Note: **If you cannot easily pull out the dosing button or dial the dose, do not use excessive force and do not use this pen because it may not deliver the correct dose.**

Step 3: Injecting the solution

- Select the injection site. Your doctor will have told you which sites to use (e.g., thigh or abdomen).

Note: change your injection site each time.

- Clean the injection site skin with the second cleansing swab.

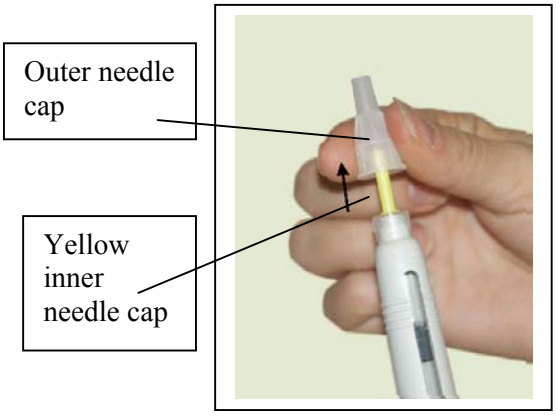


Figure 6

- Pull off the **outer needle cap**.
- There may be some liquid around the inner needle cap. This liquid is not part of your dose, this is extra. This is normal, as the air has been expelled out of the needle.
- Once the injection site is dry, pull off the **yellow inner needle cap** carefully exposing the injection needle.

Figure 7

- Hold the PegIntron pre-filled pen with your fingers wrapped around the barrel and your thumb on the dosing button.
- With your other hand, pinch a fold of loose skin.
- Insert the needle into the pinched skin at an angle of 45° to 90°.
- Press the dosing button down **slowly** and **firmly** until the button can no longer move.
- **Maintain pressure on the dosing button for an additional 5 seconds** to ensure that you get the complete dose.

- Remove the needle from your skin.
- Press the injection site with a small bandage or sterile gauze if necessary for a few seconds.
- Do not massage the injection site. If there is bleeding, cover with an adhesive bandage.
- Discard the PegIntron pre-filled pen with the needle safely in a closed rigid container.

PACKAGE LEAFLET

Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

In this leaflet:

PegIntron 80 micrograms powder and solvent for solution for injection in pre-filled pen
Peginterferon alfa-2b (conjugation of recombinant interferon alfa-2b with monomethoxy polyethylene glycol)

- The active substance is peginterferon alfa-2b, 80 micrograms/0.5 ml.
- The other ingredients are:
  Powder: disodium phosphate, anhydrous; sodium dihydrogen phosphate dihydrate, sucrose and polysorbate 80;
  Solvent: water for injections

Marketing Authorisation Holder: SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

Manufacturer: SP (Brinny) Company, Innishannon, County Cork, Ireland

1. WHAT PEGINTRON IS AND WHAT IT IS USED FOR

The pharmaceutical form is: powder and solvent for solution for injection.
The white powder and the clear and colourless solvent are both contained in a two-chamber glass cartridge assembled into a single use pre-filled pen.

PegIntron 80 micrograms is available in different pack sizes:
- 1 pen containing powder and solvent for solution for injection, 1 injection needle and 2 cleansing swabs;
- 4 pens containing powder and solvent for solution for injection, 4 injection needles and 8 cleansing swabs;
- 6 pens containing powder and solvent for solution for injection, 6 injection needles and 12 cleansing swabs;
- 12 pens containing powder and solvent for solution for injection, 12 injection needles and 24 cleansing swabs.

Not all pack sizes may be marketed.

Interferons modify the response of the body's immune system to help fight infections and severe diseases. PegIntron, which contains an interferon, is used for the treatment of chronic hepatitis C, a viral infection of the liver.

PegIntron is best used for this treatment in combination with ribavirin.

PegIntron is used alone in case of intolerance or contraindication to ribavirin.

2. BEFORE YOU USE PEGINTRON

PegIntron is not recommended for use in patients under the age of 18 years.

Do not use PegIntron:
- If you are hypersensitive (allergic) to peginterferon alfa-2b or any of the other ingredients of PegIntron.
- If you are hypersensitive (allergic) to any interferon.
- If you are pregnant or breast feeding.
- If you have had severe heart problems, or if you have heart disease that has not been well controlled during the past 6 months.
- If you have severe medical conditions that leave you very weak, including severe kidney disease.
- If you have autoimmune hepatitis or any other problem with your immune system; if you are taking medicine that suppresses your immune system (your immune system protects you against infection and some diseases).
- If you have advanced, uncontrolled liver disease (other than hepatitis C).
- If you have thyroid disease that is not well controlled with medicines.
- If you have a condition that causes convulsions (seizures, or "fits").

Take special care with PegIntron:
- If you develop symptoms of a severe allergic reaction (such as difficulty in breathing, wheezing, or hives) while on this medication, seek medical help immediately.
- If you ever had a heart attack or a heart problem.
- If you have ever been treated for depression or any other nervous or mental disorder.
- If you have had a problem with your liver (other than hepatitis C).
- If you develop symptoms associated with a cold or other respiratory infection, such as fever, cough, or any difficulty in breathing, tell your doctor.
- If you are diabetic, your doctor may ask you to have an eye examination.
- If you have had any serious illness affecting your breathing or your blood.
- If you have psoriasis, it may become worse while you are using PegIntron.
- If you are planning to become pregnant, discuss this with your doctor before starting to use PegIntron.
- If you are also being treated for HIV, please see **Using other medicines**.
- If you have had a severe nervous or mental disorder.
- If you have received an organ transplant, either kidney or liver, interferon treatment may increase the risk of rejection. Be sure to discuss this with your doctor.

While being treated with PegIntron
Your doctor may want you to drink extra fluids to help prevent low blood pressure.

Pregnancy
Ask your doctor or pharmacist for advice before taking any medicine. Do not use PegIntron during pregnancy. The effect on human pregnancy is not known.

Breast-feeding
Ask your doctor or pharmacist for advice before taking any medicine. It is not known whether this product is present in human milk. Therefore, do not breast-feed an infant if you are taking PegIntron.

Driving and using machines:
Do not drive or operate any tools or machines if you feel tired, sleepy or confused while taking PegIntron.

Using other medicines:
Please inform your doctor or pharmacist if you are taking or have recently taken any other medicines, even those not prescribed.

Important information about some of the ingredients of PegIntron:
This medicinal product contains less than 1 mmol sodium (23 mg) per 0.7 ml, i.e., essentially "sodium-free".

Patients who also have HIV infection:
Lactic acidosis and worsening liver function are side effects associated with Highly Active Anti-Retroviral Therapy (HAART), an HIV treatment. If you are receiving HAART, the addition of PegIntron and ribavirin may increase your risk of lactic acidosis and of liver failure. Your doctor will monitor you for signs and symptoms of these conditions. (Please be sure to read the ribavirin Patient Leaflet also).

3. HOW TO USE PEGINTRON

Your doctor has prescribed PegIntron specifically for you and your current condition; do not share this medicine with anyone else.

Your doctor has determined your dose of PegIntron based on your weight. If necessary, the dose may be changed during treatment.

Combination treatment
PegIntron, when given with ribavirin capsules, is usually given at a dose of 1.5 microgram/kg once a week.

Ribavirin capsules are taken every day, morning and evening. The number of ribavirin capsules you take depends on your weight.
- If you weigh less than 65 kg, take 2 capsules in the morning and 2 in the evening (total of 800 mg each day).
- If you weigh between 65 and 85 kg, take 2 capsules in the morning and 3 in the evening (total of 1,000 mg each day).
- If you weigh more than 85 kg, take 3 capsules in the morning and 3 in the evening (total 1,200 mg each day).

The combination treatment is continued for at least 6 months, and sometimes for one year.

PegIntron alone:
PegIntron, when given alone, is usually given at a dose of 0.5 or 1.0 microgram/kg once a week, for at least 6 months, and possibly for 1 year.

All patients:
If you are injecting PegIntron yourself, please be sure that the dose that has been prescribed for you is clearly provided on the package of medicine you receive.

If you have the impression that the effect of PegIntron is too strong or too weak, talk to your doctor or pharmacist.

PegIntron is intended for subcutaneous use. This means that it is injected through a short injection needle into the fatty tissue just under your skin. If you are injecting this medicine yourself, you will be instructed how to prepare and give the injection. Detailed instructions for subcutaneous administration are provided with this leaflet (see How to use the PegIntron pre-filled pen).

Prepare the dose just before you intend to inject it and use it immediately. Look carefully at the reconstituted solution prior to administration. Do not use if there is discolouration of the reconstituted solution or if particulate matter is present. PegIntron is intended for single use only. Thus, after you give yourself the injection, discard the PegIntron pre-filled pen with any solution that is left in it.

Inject PegIntron once each week on the same day. Injecting it at the same time of day each week will help you not to forget to take it.

Use PegIntron exactly as prescribed by your doctor. Do not exceed the recommended dosage, and take it for as long as prescribed.

If you use more PegIntron than you should:
Tell your doctor or healthcare professional as soon as possible.

If you forget to take PegIntron:
Take the dose as soon as you remember, then continue your treatment as usual.
Do not take a double dose to make up for forgotten individual doses. Contact your doctor or pharmacist if needed.

4. POSSIBLE SIDE EFFECTS

Like all medicines, PegIntron can have side effects. Although not all of these side effects may occur, they may need medical attention if they do.

Check with your doctor immediately if any of the following side effects occur: chest pain; changes in the way your heart beats; breathing problems, (including shortness of breath), confusion; feeling depressed, wanting to harm yourself, hallucinations, numbness or tingling feeling; dizziness, convulsion ("fit"); trouble sleeping, thinking or concentrating; difficulty remaining alert, severe stomach pain or cramps; blood or clots in stool (or black, tarry stool); fever or chills beginning after a few weeks of treatment, pain in your lower back or side; difficulty or inability to pass urine, painful or inflamed muscles (sometimes severe); problems with your eyes or your eyesight or hearing; severe or painful reddening of your skin or mucous membrane, severe bleeding from your nose. Your doctor will test your blood to ensure that your white blood cell (cells that fight infection) and red blood cell (cells that carry oxygen) counts, platelets (blood clotting cells) and other laboratory values are at acceptable levels.

Some people get depressed when taking PegIntron alone or in combination treatment with ribavirin, and in some cases people had suicidal thoughts or aggressive behaviour. Some patients have actually committed suicide. Be sure to seek emergency care if you notice that you are becoming depressed or have suicidal thoughts or change in your behaviour. You may want to consider asking a family member or close friend to help you stay alert to signs of depression or changes in your behaviour.

The most common side effects with the combination of PegIntron and ribavirin capsules are irritation or redness (and rarely, skin damage) at the site of injection, headache, tired feeling, shaking chills, fever, flu-like symptoms, weakness, loss of weight, nausea, loss of appetite, diarrhoea or loose stools, stomach pain, vomiting, muscle aches, pain in joints and muscles, feeling depressed, irritability, trouble falling asleep or staying asleep, feeling anxious or nervous, difficulty concentrating, mood swings, hair loss, itching, dry skin, sore throat, coughing, difficult breathing, dizziness, virus infection, rash, and dry mouth.

Other common side effects that may occur with combination treatment are increased sweating, chest pain, pain on the right side around your ribs, numbness, pain or tingling feeling, change in thyroid gland activity (which may make you feel tired or, less commonly, energetic), stomach upset, rapid heart rate, agitation, nervousness, difficult or irregular menstrual period.

Less common are pain at the place of injection, flushing, low or high blood pressure, dry or teary eyes, redness of skin or skin disorder, psoriasis, hives, nail disorder, feeling unwell, feeling faint, poor coordination, confusion, increased or decreased sensitivity to touch, tense muscles, arthritis, bruising, loss of interest in activities including sex, sexual problem, unusual dreams, shaky hands, vertigo (spinning feeling), increased appetite, heartburn, intestinal gas (flatus), constipation, hemorrhoids, red or bleeding gums, redness or sores in mouth, change in taste, changes in hearing or ringing in ears, thirst, aggressive or changed behaviour, feeling sleepy, cold sores, fungal or bacterial infections, irritation of prostate gland,

increased need to pass urine, ear or respiratory infections, sinusitis, stuffy or runny nose, abnormal hair texture, sensitivity to sunlight, migraine headache, eye pain or infection, blurred vision, puffy face, puffy hands or feet, enlarged liver, problem affecting ovary or vagina, pain in breast, difficulty in speaking, diabetes and swollen glands.

Very rarely sarcoidosis (a disease characterised by persistent fever, weight loss, joint pain and swelling, skin lesions and swollen glands) has been reported. Loss of consciousness has occurred very rarely with alpha interferons, mostly in elderly patients treated at high doses. Cases of stroke (cerebrovascular events) have been reported. Check with your doctor immediately if you have any of these symptoms or any other symptoms that are troubling.

Very rarely, PegIntron alone or in combination with ribavirin may cause aplastic anaemia.

When PegIntron is used alone, some of these effects are less likely to occur, and some have not occurred at all.

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

5. STORING PEGINTRON

Keep out of the reach and sight of children.

Store in a refrigerator (2°C - 8°C). Do not freeze.

Do not use after the expiry date stated on the carton.
After reconstitution, use the reconstituted solution immediately or within 24 hours when stored at 2°C - 8°C (in a refrigerator).

Do not use PegIntron if you notice discolouration of the reconstituted solution.

6. FURTHER INFORMATION

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

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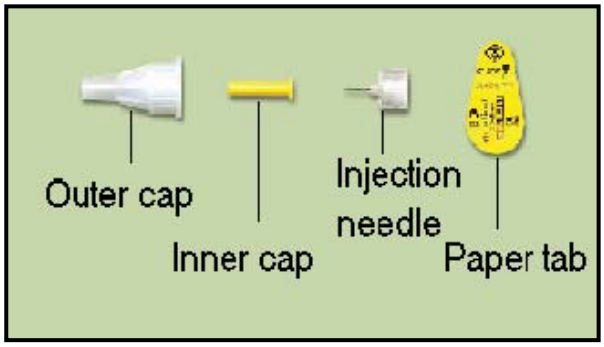
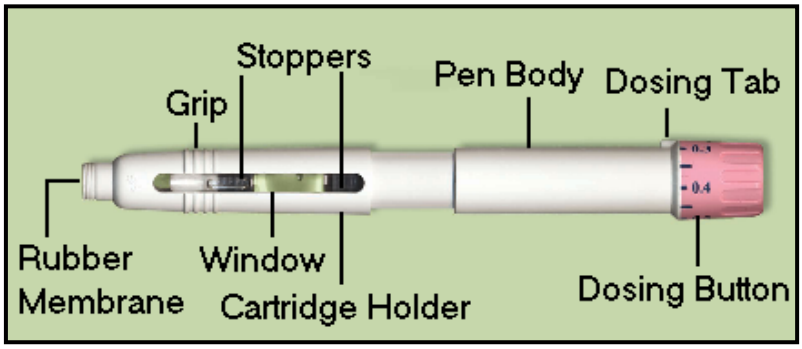
ANNEX TO THE PACKAGE LEAFLET

How to use the PegIntron pre-filled pen





The following instructions explain how to inject yourself with the single use PegIntron pre-filled pen. **Please read the instructions carefully and completely before attempting to use the pen and follow them step by step.** Your doctor or his/her assistant will instruct you on how to self-inject with the PegIntron pre-filled pen. Do not attempt to inject yourself unless you are sure you understand the procedure and requirements for self-injection.

The PegIntron pre-filled pen is intended for use by one person only and must not be shared. Use the injection needle and cleansing swabs provided in the packaging only for the PegIntron pre-filled pen. Be sure the solution is at room temperature at the time of injection. Your doctor will have told you what dose you require for your therapy.

Note: The colour of the dosing button is different for each strength of the PegIntron pre-filled pen.

Step 1: Mixing

It is important that you keep the PegIntron pre-filled pen upright (as shown in figure 1) during mixing, unless otherwise instructed.

- Take the PegIntron pre-filled pen out of the refrigerator. Allow the medicine to come to room temperature.

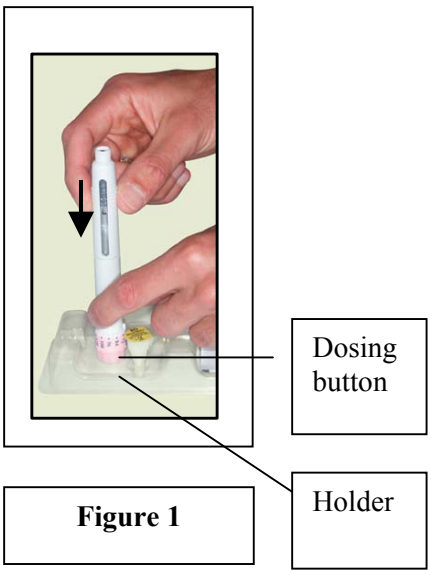
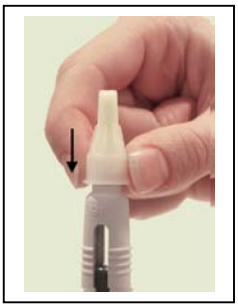


Figure 1

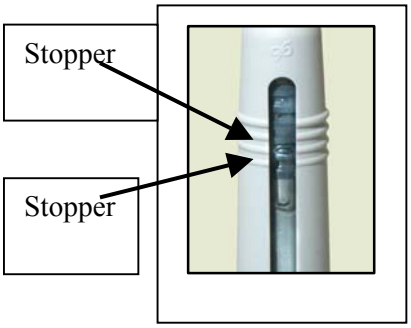
- Wash your hands with soap and water.
- **Place the PegIntron pre-filled pen upright** in the holder of the tray provided in the pack (the dosing button will be on the **bottom**).
- You may want to hold the pre-filled pen using the grip. To mix the powder and the liquid, press the two halves together firmly by pressing down until you hear the pre-filled pen click. The two stoppers should come together.
- Wait for several seconds until the powder is completely dissolved.
- **Gently turn the PegIntron pre-filled pen upside down twice. To avoid excessive foaming, do not shake.**
- Maintaining the PegIntron pre-filled pen upright, check the mixed PegIntron solution through the window. If there is still foam, wait until it settles. The solution should be clear and colourless. **Do not use the pen if the solution is discoloured or contains any particles.**



- Keeping the PegIntron pre-filled pen upright in the holder provided in the packaging, disinfect the rubber membrane of the PegIntron pre-filled pen with one cleansing swab.
- Take the injection needle provided in the tray and remove its protective paper tab.
- **Maintaining the PegIntron pre-filled pen upright in the holder,** gently push the injection needle onto the pre-filled pen and **screw it securely in place**.

Figure 2

- **Keep the PegIntron pre-filled pen pointed up**.
- **Do not take off the outer needle cap at this point.**
- You may see some liquid trickle out from under the cap, as the air has been expelled out of the pen.
- Wait about 5 seconds for this process to finish.



- **Check through the window to be sure that the two stoppers are together. If they are not together, do not use this pen because you may not be able to dial your dose.**

Figure 3

Step 2: Setting the dose

- Remove the PegIntron pre-filled pen from the holder.
- Holding the PegIntron pre-filled pen firmly, pull the dosing button out as far as it will go, until you see a **dark ring** on the pen. The dosing button should be easy to pull out without excessive force being required.

Note: Do not push the dosing button back in at this time. You will push it in when you are ready to self-inject the PegIntron.

Figure 4

Figure 5

- Turn the dosing button until your prescribed dose is aligned with the dosing tab. The button should turn easily without excessive force being required.

Note: **If you cannot easily pull out the dosing button or dial the dose, do not use excessive force and do not use this pen because it may not deliver the correct dose.**

Step 3: Injecting the solution

- Select the injection site. Your doctor will have told you which sites to use (e.g., thigh or abdomen).

Note: change your injection site each time.

- Clean the injection site skin with the second cleansing swab.

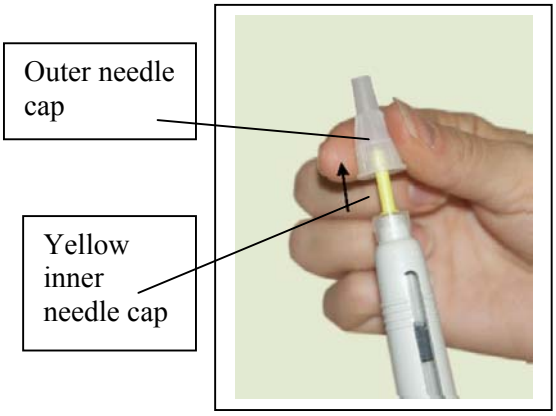


Figure 6

- Pull off the **outer needle cap**.
- There may be some liquid around the inner needle cap. This liquid is not part of your dose, this is extra. This is normal, as the air has been expelled out of the needle.
- Once the injection site is dry, pull off the **yellow inner needle cap** carefully exposing the injection needle.

Figure 7

- Hold the PegIntron pre-filled pen with your fingers wrapped around the barrel and your thumb on the dosing button.
- With your other hand, pinch a fold of loose skin.
- Insert the needle into the pinched skin at an angle of 45° to 90°.
- Press the dosing button down **slowly** and **firmly** until the button can no longer move.
- **Maintain pressure on the dosing button for an additional 5 seconds** to ensure that you get the complete dose.

- Remove the needle from your skin.
- Press the injection site with a small bandage or sterile gauze if necessary for a few seconds.
- Do not massage the injection site. If there is bleeding, cover with an adhesive bandage.
- Discard the PegIntron pre-filled pen with the needle safely in a closed rigid container.

PACKAGE LEAFLET

Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

In this leaflet:

PegIntron 100 micrograms powder and solvent for solution for injection in pre-filled pen
Peginterferon alfa-2b (conjugation of recombinant interferon alfa-2b with monomethoxy polyethylene glycol)

- The active substance is peginterferon alfa-2b, 100 micrograms/0.5 ml.
- The other ingredients are:
  Powder: disodium phosphate, anhydrous; sodium dihydrogen phosphate dihydrate, sucrose and polysorbate 80;
  Solvent: water for injections

Marketing Authorisation Holder: SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

Manufacturer: SP (Brinny) Company, Innishannon, County Cork, Ireland

1. WHAT PEGINTRON IS AND WHAT IT IS USED FOR

The pharmaceutical form is: powder and solvent for solution for injection.
The white powder and the clear and colourless solvent are both contained in a two-chamber glass cartridge assembled into a single use pre-filled pen.

PegIntron 100 micrograms is available in different pack sizes:
- 1 pen containing powder and solvent for solution for injection, 1 injection needle and 2 cleansing swabs;
- 4 pens containing powder and solvent for solution for injection, 4 injection needles and 8 cleansing swabs;
- 6 pens containing powder and solvent for solution for injection, 6 injection needles and 12 cleansing swabs;
- 12 pens containing powder and solvent for solution for injection, 12 injection needles and 24 cleansing swabs.

Not all pack sizes may be marketed.

Interferons modify the response of the body's immune system to help fight infections and severe diseases. PegIntron, which contains an interferon, is used for the treatment of chronic hepatitis C, a viral infection of the liver.

PegIntron is best used for this treatment in combination with ribavirin.

PegIntron is used alone in case of intolerance or contraindication to ribavirin.

2. BEFORE YOU USE PEGINTRON

PegIntron is not recommended for use in patients under the age of 18 years.

Do not use PegIntron:
- If you are hypersensitive (allergic) to peginterferon alfa-2b or any of the other ingredients of PegIntron.
- If you are hypersensitive (allergic) to any interferon.
- If you are pregnant or breast feeding.
- If you have had severe heart problems, or if you have heart disease that has not been well controlled during the past 6 months.
- If you have severe medical conditions that leave you very weak, including severe kidney disease.
- If you have autoimmune hepatitis or any other problem with your immune system; if you are taking medicine that suppresses your immune system (your immune system protects you against infection and some diseases).
- If you have advanced, uncontrolled liver disease (other than hepatitis C).
- If you have thyroid disease that is not well controlled with medicines.
- If you have a condition that causes convulsions (seizures, or "fits").

Take special care with PegIntron:
- If you develop symptoms of a severe allergic reaction (such as difficulty in breathing, wheezing, or hives) while on this medication, seek medical help immediately.
- If you ever had a heart attack or a heart problem.
- If you have ever been treated for depression or any other nervous or mental disorder.
- If you have had a problem with your liver (other than hepatitis C).
- If you develop symptoms associated with a cold or other respiratory infection, such as fever, cough, or any difficulty in breathing, tell your doctor.
- If you are diabetic, your doctor may ask you to have an eye examination.
- If you have had any serious illness affecting your breathing or your blood.
- If you have psoriasis, it may become worse while you are using PegIntron.
- If you are planning to become pregnant, discuss this with your doctor before starting to use PegIntron.
- If you are also being treated for HIV, please see **Using other medicines**.
- If you have had a severe nervous or mental disorder.
- If you have received an organ transplant, either kidney or liver, interferon treatment may increase the risk of rejection. Be sure to discuss this with your doctor.

While being treated with PegIntron
Your doctor may want you to drink extra fluids to help prevent low blood pressure.

Pregnancy
Ask your doctor or pharmacist for advice before taking any medicine. Do not use PegIntron during pregnancy. The effect on human pregnancy is not known.

Breast-feeding
Ask your doctor or pharmacist for advice before taking any medicine. It is not known whether this product is present in human milk. Therefore, do not breast-feed an infant if you are taking PegIntron.

Driving and using machines:
Do not drive or operate any tools or machines if you feel tired, sleepy or confused while taking PegIntron.

Using other medicines:
Please inform your doctor or pharmacist if you are taking or have recently taken any other medicines, even those not prescribed.

Important information about some of the ingredients of PegIntron:
This medicinal product contains less than 1 mmol sodium (23 mg) per 0.7 ml, i.e., essentially "sodium-free".

Patients who also have HIV infection:
Lactic acidosis and worsening liver function are side effects associated with Highly Active Anti-Retroviral Therapy (HAART), an HIV treatment. If you are receiving HAART, the addition of PegIntron and ribavirin may increase your risk of lactic acidosis and of liver failure. Your doctor will monitor you for signs and symptoms of these conditions. (Please be sure to read the ribavirin Patient Leaflet also).

3. HOW TO USE PEGINTRON

Your doctor has prescribed PegIntron specifically for you and your current condition; do not share this medicine with anyone else.

Your doctor has determined your dose of PegIntron based on your weight. If necessary, the dose may be changed during treatment.

Combination treatment
PegIntron, when given with ribavirin capsules, is usually given at a dose of 1.5 microgram/kg once a week.

Ribavirin capsules are taken every day, morning and evening. The number of ribavirin capsules you take depends on your weight.
- If you weigh less than 65 kg, take 2 capsules in the morning and 2 in the evening (total of 800 mg each day).
- If you weigh between 65 and 85 kg, take 2 capsules in the morning and 3 in the evening (total of 1,000 mg each day).
- If you weigh more than 85 kg, take 3 capsules in the morning and 3 in the evening (total 1,200 mg each day).

The combination treatment is continued for at least 6 months, and sometimes for one year.

PegIntron alone:
PegIntron, when given alone, is usually given at a dose of 0.5 or 1.0 microgram/kg once a week, for at least 6 months, and possibly for 1 year.

All patients:
If you are injecting PegIntron yourself, please be sure that the dose that has been prescribed for you is clearly provided on the package of medicine you receive.

If you have the impression that the effect of PegIntron is too strong or too weak, talk to your doctor or pharmacist.

PegIntron is intended for subcutaneous use. This means that it is injected through a short injection needle into the fatty tissue just under your skin. If you are injecting this medicine yourself, you will be instructed how to prepare and give the injection. Detailed instructions for subcutaneous administration are provided with this leaflet (see How to use the PegIntron pre-filled pen).

Prepare the dose just before you intend to inject it and use it immediately. Look carefully at the reconstituted solution prior to administration. Do not use if there is discolouration of the reconstituted solution or if particulate matter is present. PegIntron is intended for single use only. Thus, after you give yourself the injection, discard the PegIntron pre-filled pen with any solution that is left in it.

Inject PegIntron once each week on the same day. Injecting it at the same time of day each week will help you not to forget to take it.

Use PegIntron exactly as prescribed by your doctor. Do not exceed the recommended dosage, and take it for as long as prescribed.

If you use more PegIntron than you should:
Tell your doctor or healthcare professional as soon as possible.

If you forget to take PegIntron:
Take the dose as soon as you remember, then continue your treatment as usual.
Do not take a double dose to make up for forgotten individual doses. Contact your doctor or pharmacist if needed.

4. POSSIBLE SIDE EFFECTS

Like all medicines, PegIntron can have side effects. Although not all of these side effects may occur, they may need medical attention if they do.

Check with your doctor immediately if any of the following side effects occur: chest pain; changes in the way your heart beats; breathing problems, (including shortness of breath), confusion; feeling depressed, wanting to harm yourself, hallucinations, numbness or tingling feeling; dizziness, convulsion ("fit"); trouble sleeping, thinking or concentrating; difficulty remaining alert, severe stomach pain or cramps; blood or clots in stool (or black, tarry stool); fever or chills beginning after a few weeks of treatment, pain in your lower back or side; difficulty or inability to pass urine, painful or inflamed muscles (sometimes severe); problems with your eyes or your eyesight or hearing; severe or painful reddening of your skin or mucous membrane, severe bleeding from your nose. Your doctor will test your blood to ensure that your white blood cell (cells that fight infection) and red blood cell (cells that carry oxygen) counts, platelets (blood clotting cells) and other laboratory values are at acceptable levels.

Some people get depressed when taking PegIntron alone or in combination treatment with ribavirin, and in some cases people had suicidal thoughts or aggressive behaviour. Some patients have actually committed suicide. Be sure to seek emergency care if you notice that you are becoming depressed or have suicidal thoughts or change in your behaviour. You may want to consider asking a family member or close friend to help you stay alert to signs of depression or changes in your behaviour.

The most common side effects with the combination of PegIntron and ribavirin capsules are irritation or redness (and rarely, skin damage) at the site of injection, headache, tired feeling, shaking chills, fever, flu-like symptoms, weakness, loss of weight, nausea, loss of appetite, diarrhoea or loose stools, stomach pain, vomiting, muscle aches, pain in joints and muscles, feeling depressed, irritability, trouble falling asleep or staying asleep, feeling anxious or nervous, difficulty concentrating, mood swings, hair loss, itching, dry skin, sore throat, coughing, difficult breathing, dizziness, virus infection, rash, and dry mouth.

Other common side effects that may occur with combination treatment are increased sweating, chest pain, pain on the right side around your ribs, numbness, pain or tingling feeling, change in thyroid gland activity (which may make you feel tired or, less commonly, energetic), stomach upset, rapid heart rate, agitation, nervousness, difficult or irregular menstrual period.

Less common are pain at the place of injection, flushing, low or high blood pressure, dry or teary eyes, redness of skin or skin disorder, psoriasis, hives, nail disorder, feeling unwell, feeling faint, poor coordination, confusion, increased or decreased sensitivity to touch, tense muscles, arthritis, bruising, loss of interest in activities including sex, sexual problem, unusual dreams, shaky hands, vertigo (spinning feeling), increased appetite, heartburn, intestinal gas (flatus), constipation, hemorrhoids, red or bleeding gums, redness or sores in mouth, change in taste, changes in hearing or ringing in ears, thirst, aggressive or changed behaviour, feeling sleepy, cold sores, fungal or bacterial infections, irritation of prostate gland,

increased need to pass urine, ear or respiratory infections, sinusitis, stuffy or runny nose, abnormal hair texture, sensitivity to sunlight, migraine headache, eye pain or infection, blurred vision, puffy face, puffy hands or feet, enlarged liver, problem affecting ovary or vagina, pain in breast, difficulty in speaking, diabetes and swollen glands.

Very rarely sarcoidosis (a disease characterised by persistent fever, weight loss, joint pain and swelling, skin lesions and swollen glands) has been reported. Loss of consciousness has occurred very rarely with alpha interferons, mostly in elderly patients treated at high doses. Cases of stroke (cerebrovascular events) have been reported. Check with your doctor immediately if you have any of these symptoms or any other symptoms that are troubling.

Very rarely, PegIntron alone or in combination with ribavirin may cause aplastic anaemia.

When PegIntron is used alone, some of these effects are less likely to occur, and some have not occurred at all.

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

5. STORING PEGINTRON

Keep out of the reach and sight of children.

Store in a refrigerator (2°C - 8°C). Do not freeze.

Do not use after the expiry date stated on the carton.
After reconstitution, use the reconstituted solution immediately or within 24 hours when stored at 2°C - 8°C (in a refrigerator).

Do not use PegIntron if you notice discolouration of the reconstituted solution.

6. FURTHER INFORMATION

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

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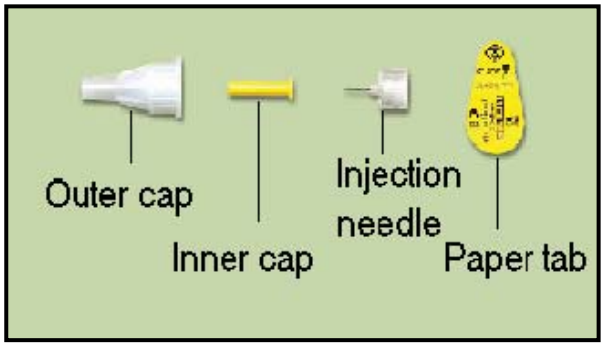

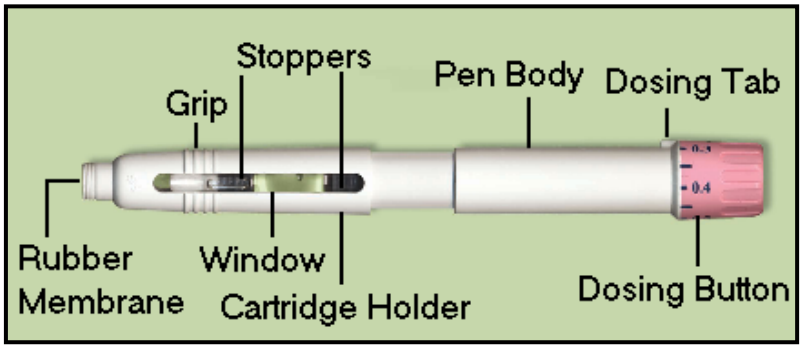

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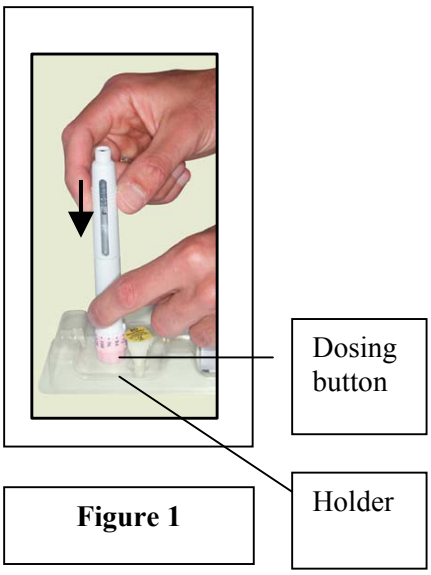

Figure 1

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- Wait for several seconds until the powder is completely dissolved.
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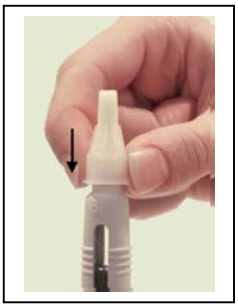
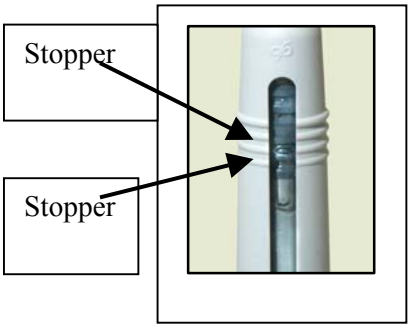
- Maintaining the PegIntron pre-filled pen upright, check the mixed PegIntron solution through the window. If there is still foam, wait until it settles. The solution should be clear and colourless. **Do not use the pen if the solution is discoloured or contains any particles.**



- Keeping the PegIntron pre-filled pen upright in the holder provided in the packaging, disinfect the rubber membrane of the PegIntron pre-filled pen with one cleansing swab.
- Take the injection needle provided in the tray and remove its protective paper tab.
- **Maintaining the PegIntron pre-filled pen upright in the holder,** gently push the injection needle onto the pre-filled pen and **screw it securely in place**.

Figure 2

- **Keep the PegIntron pre-filled pen pointed up**.
- **Do not take off the outer needle cap at this point.**
- You may see some liquid trickle out from under the cap, as the air has been expelled out of the pen.
- Wait about 5 seconds for this process to finish.



- **Check through the window to be sure that the two stoppers are together. If they are not together, do not use this pen because you may not be able to dial your dose.**

Figure 3

Step 2: Setting the dose

- Remove the PegIntron pre-filled pen from the holder.
- Holding the PegIntron pre-filled pen firmly, pull the dosing button out as far as it will go, until you see a **dark ring** on the pen. The dosing button should be easy to pull out without excessive force being required.

Note: Do not push the dosing button back in at this time. You will push it in when you are ready to self-inject the PegIntron.

Figure 4

Figure 5

- Turn the dosing button until your prescribed dose is aligned with the dosing tab. The button should turn easily without excessive force being required.

Note: **If you cannot easily pull out the dosing button or dial the dose, do not use excessive force and do not use this pen because it may not deliver the correct dose.**

Step 3: Injecting the solution

- Select the injection site. Your doctor will have told you which sites to use (e.g., thigh or abdomen).

Note: change your injection site each time.

- Clean the injection site skin with the second cleansing swab.

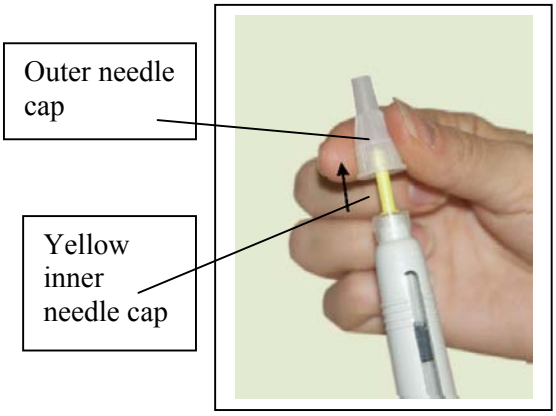


Figure 6

- Pull off the **outer needle cap**.
- There may be some liquid around the inner needle cap. This liquid is not part of your dose, this is extra. This is normal, as the air has been expelled out of the needle.
- Once the injection site is dry, pull off the **yellow inner needle cap** carefully exposing the injection needle.

Figure 7

- Hold the PegIntron pre-filled pen with your fingers wrapped around the barrel and your thumb on the dosing button.
- With your other hand, pinch a fold of loose skin.
- Insert the needle into the pinched skin at an angle of 45° to 90°.
- Press the dosing button down **slowly** and **firmly** until the button can no longer move.
- **Maintain pressure on the dosing button for an additional 5 seconds** to ensure that you get the complete dose.

- Remove the needle from your skin.
- Press the injection site with a small bandage or sterile gauze if necessary for a few seconds.
- Do not massage the injection site. If there is bleeding, cover with an adhesive bandage.
- Discard the PegIntron pre-filled pen with the needle safely in a closed rigid container.

PACKAGE LEAFLET

Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

In this leaflet:

PegIntron 120 micrograms powder and solvent for solution for injection in pre-filled pen
Peginterferon alfa-2b (conjugation of recombinant interferon alfa-2b with monomethoxy polyethylene glycol)

- The active substance is peginterferon alfa-2b, 120 micrograms/0.5 ml.
- The other ingredients are:
  Powder: disodium phosphate, anhydrous; sodium dihydrogen phosphate dihydrate, sucrose and polysorbate 80;
  Solvent: water for injections

Marketing Authorisation Holder: SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

Manufacturer: SP (Brinny) Company, Innishannon, County Cork, Ireland

1. WHAT PEGINTRON IS AND WHAT IT IS USED FOR

The pharmaceutical form is: powder and solvent for solution for injection.
The white powder and the clear and colourless solvent are both contained in a two-chamber glass cartridge assembled into a single use pre-filled pen.

PegIntron 120 micrograms is available in different pack sizes:
- 1 pen containing powder and solvent for solution for injection, 1 injection needle and 2 cleansing swabs;
- 4 pens containing powder and solvent for solution for injection, 4 injection needles and 8 cleansing swabs;
- 6 pens containing powder and solvent for solution for injection, 6 injection needles and 12 cleansing swabs;
- 12 pens containing powder and solvent for solution for injection, 12 injection needles and 24 cleansing swabs.

Not all pack sizes may be marketed.

Interferons modify the response of the body's immune system to help fight infections and severe diseases. PegIntron, which contains an interferon, is used for the treatment of chronic hepatitis C, a viral infection of the liver.

PegIntron is best used for this treatment in combination with ribavirin.

PegIntron is used alone in case of intolerance or contraindication to ribavirin.

2. BEFORE YOU USE PEGINTRON

PegIntron is not recommended for use in patients under the age of 18 years.

Do not use PegIntron:
- If you are hypersensitive (allergic) to peginterferon alfa-2b or any of the other ingredients of PegIntron.
- If you are hypersensitive (allergic) to any interferon.
- If you are pregnant or breast feeding.
- If you have had severe heart problems, or if you have heart disease that has not been well controlled during the past 6 months.
- If you have severe medical conditions that leave you very weak, including severe kidney disease.
- If you have autoimmune hepatitis or any other problem with your immune system; if you are taking medicine that suppresses your immune system (your immune system protects you against infection and some diseases).
- If you have advanced, uncontrolled liver disease (other than hepatitis C).
- If you have thyroid disease that is not well controlled with medicines.
- If you have a condition that causes convulsions (seizures, or "fits").

Take special care with PegIntron:
- If you develop symptoms of a severe allergic reaction (such as difficulty in breathing, wheezing, or hives) while on this medication, seek medical help immediately.
- If you ever had a heart attack or a heart problem.
- If you have ever been treated for depression or any other nervous or mental disorder.
- If you have had a problem with your liver (other than hepatitis C).
- If you develop symptoms associated with a cold or other respiratory infection, such as fever, cough, or any difficulty in breathing, tell your doctor.
- If you are diabetic, your doctor may ask you to have an eye examination.
- If you have had any serious illness affecting your breathing or your blood.
- If you have psoriasis, it may become worse while you are using PegIntron.
- If you are planning to become pregnant, discuss this with your doctor before starting to use PegIntron.
- If you are also being treated for HIV, please see **Using other medicines**.
- If you have had a severe nervous or mental disorder.
- If you have received an organ transplant, either kidney or liver, interferon treatment may increase the risk of rejection. Be sure to discuss this with your doctor.

While being treated with PegIntron
Your doctor may want you to drink extra fluids to help prevent low blood pressure.

Pregnancy
Ask your doctor or pharmacist for advice before taking any medicine. Do not use PegIntron during pregnancy. The effect on human pregnancy is not known.

Breast-feeding
Ask your doctor or pharmacist for advice before taking any medicine. It is not known whether this product is present in human milk. Therefore, do not breast-feed an infant if you are taking PegIntron.

Driving and using machines:
Do not drive or operate any tools or machines if you feel tired, sleepy or confused while taking PegIntron.

Using other medicines:
Please inform your doctor or pharmacist if you are taking or have recently taken any other medicines, even those not prescribed.

Important information about some of the ingredients of PegIntron:
This medicinal product contains less than 1 mmol sodium (23 mg) per 0.7 ml, i.e., essentially "sodium-free".

Patients who also have HIV infection:
Lactic acidosis and worsening liver function are side effects associated with Highly Active Anti-Retroviral Therapy (HAART), an HIV treatment. If you are receiving HAART, the addition of PegIntron and ribavirin may increase your risk of lactic acidosis and of liver failure. Your doctor will monitor you for signs and symptoms of these conditions. (Please be sure to read the ribavirin Patient Leaflet also).

3. HOW TO USE PEGINTRON

Your doctor has prescribed PegIntron specifically for you and your current condition; do not share this medicine with anyone else.

Your doctor has determined your dose of PegIntron based on your weight. If necessary, the dose may be changed during treatment.

Combination treatment
PegIntron, when given with ribavirin capsules, is usually given at a dose of 1.5 microgram/kg once a week.

Ribavirin capsules are taken every day, morning and evening. The number of ribavirin capsules you take depends on your weight.
- If you weigh less than 65 kg, take 2 capsules in the morning and 2 in the evening (total of 800 mg each day).
- If you weigh between 65 and 85 kg, take 2 capsules in the morning and 3 in the evening (total of 1,000 mg each day).
- If you weigh more than 85 kg, take 3 capsules in the morning and 3 in the evening (total 1,200 mg each day).

The combination treatment is continued for at least 6 months, and sometimes for one year.

PegIntron alone:
PegIntron, when given alone, is usually given at a dose of 0.5 or 1.0 microgram/kg once a week, for at least 6 months, and possibly for 1 year.

All patients:
If you are injecting PegIntron yourself, please be sure that the dose that has been prescribed for you is clearly provided on the package of medicine you receive.

If you have the impression that the effect of PegIntron is too strong or too weak, talk to your doctor or pharmacist.

PegIntron is intended for subcutaneous use. This means that it is injected through a short injection needle into the fatty tissue just under your skin. If you are injecting this medicine yourself, you will be instructed how to prepare and give the injection. Detailed instructions for subcutaneous administration are provided with this leaflet (see How to use the PegIntron pre-filled pen).

Prepare the dose just before you intend to inject it and use it immediately. Look carefully at the reconstituted solution prior to administration. Do not use if there is discolouration of the reconstituted solution or if particulate matter is present. PegIntron is intended for single use only. Thus, after you give yourself the injection, discard the PegIntron pre-filled pen with any solution that is left in it.

Inject PegIntron once each week on the same day. Injecting it at the same time of day each week will help you not to forget to take it.

Use PegIntron exactly as prescribed by your doctor. Do not exceed the recommended dosage, and take it for as long as prescribed.

If you use more PegIntron than you should:
Tell your doctor or healthcare professional as soon as possible.

If you forget to take PegIntron:
Take the dose as soon as you remember, then continue your treatment as usual.
Do not take a double dose to make up for forgotten individual doses. Contact your doctor or pharmacist if needed.

4. POSSIBLE SIDE EFFECTS

Like all medicines, PegIntron can have side effects. Although not all of these side effects may occur, they may need medical attention if they do.

Check with your doctor immediately if any of the following side effects occur: chest pain; changes in the way your heart beats; breathing problems, (including shortness of breath), confusion; feeling depressed, wanting to harm yourself, hallucinations, numbness or tingling feeling; dizziness, convulsion ("fit"); trouble sleeping, thinking or concentrating; difficulty remaining alert, severe stomach pain or cramps; blood or clots in stool (or black, tarry stool); fever or chills beginning after a few weeks of treatment, pain in your lower back or side; difficulty or inability to pass urine, painful or inflamed muscles (sometimes severe); problems with your eyes or your eyesight or hearing; severe or painful reddening of your skin or mucous membrane, severe bleeding from your nose. Your doctor will test your blood to ensure that your white blood cell (cells that fight infection) and red blood cell (cells that carry oxygen) counts, platelets (blood clotting cells) and other laboratory values are at acceptable levels.

Some people get depressed when taking PegIntron alone or in combination treatment with ribavirin, and in some cases people had suicidal thoughts or aggressive behaviour. Some patients have actually committed suicide. Be sure to seek emergency care if you notice that you are becoming depressed or have suicidal thoughts or change in your behaviour. You may want to consider asking a family member or close friend to help you stay alert to signs of depression or changes in your behaviour.

The most common side effects with the combination of PegIntron and ribavirin capsules are irritation or redness (and rarely, skin damage) at the site of injection, headache, tired feeling, shaking chills, fever, flu-like symptoms, weakness, loss of weight, nausea, loss of appetite, diarrhoea or loose stools, stomach pain, vomiting, muscle aches, pain in joints and muscles, feeling depressed, irritability, trouble falling asleep or staying asleep, feeling anxious or nervous, difficulty concentrating, mood swings, hair loss, itching, dry skin, sore throat, coughing, difficult breathing, dizziness, virus infection, rash, and dry mouth.

Other common side effects that may occur with combination treatment are increased sweating, chest pain, pain on the right side around your ribs, numbness, pain or tingling feeling, change in thyroid gland activity (which may make you feel tired or, less commonly, energetic), stomach upset, rapid heart rate, agitation, nervousness, difficult or irregular menstrual period.

Less common are pain at the place of injection, flushing, low or high blood pressure, dry or teary eyes, redness of skin or skin disorder, psoriasis, hives, nail disorder, feeling unwell, feeling faint, poor coordination, confusion, increased or decreased sensitivity to touch, tense muscles, arthritis, bruising, loss of interest in activities including sex, sexual problem, unusual dreams, shaky hands, vertigo (spinning feeling), increased appetite, heartburn, intestinal gas (flatus), constipation, hemorrhoids, red or bleeding gums, redness or sores in mouth, change in taste, changes in hearing or ringing in ears, thirst, aggressive or changed behaviour, feeling sleepy, cold sores, fungal or bacterial infections, irritation of prostate gland,

increased need to pass urine, ear or respiratory infections, sinusitis, stuffy or runny nose, abnormal hair texture, sensitivity to sunlight, migraine headache, eye pain or infection, blurred vision, puffy face, puffy hands or feet, enlarged liver, problem affecting ovary or vagina, pain in breast, difficulty in speaking, diabetes and swollen glands.

Very rarely sarcoidosis (a disease characterised by persistent fever, weight loss, joint pain and swelling, skin lesions and swollen glands) has been reported. Loss of consciousness has occurred very rarely with alpha interferons, mostly in elderly patients treated at high doses. Cases of stroke (cerebrovascular events) have been reported. Check with your doctor immediately if you have any of these symptoms or any other symptoms that are troubling.

Very rarely, PegIntron alone or in combination with ribavirin may cause aplastic anaemia.

When PegIntron is used alone, some of these effects are less likely to occur, and some have not occurred at all.

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

5. STORING PEGINTRON

Keep out of the reach and sight of children.

Store in a refrigerator (2°C - 8°C). Do not freeze.

Do not use after the expiry date stated on the carton.
After reconstitution, use the reconstituted solution immediately or within 24 hours when stored at 2°C - 8°C (in a refrigerator).

Do not use PegIntron if you notice discolouration of the reconstituted solution.

6. FURTHER INFORMATION

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

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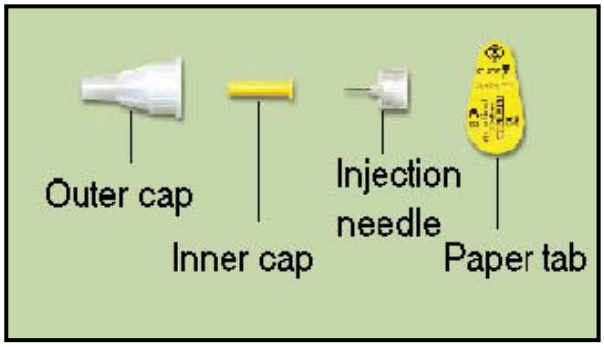
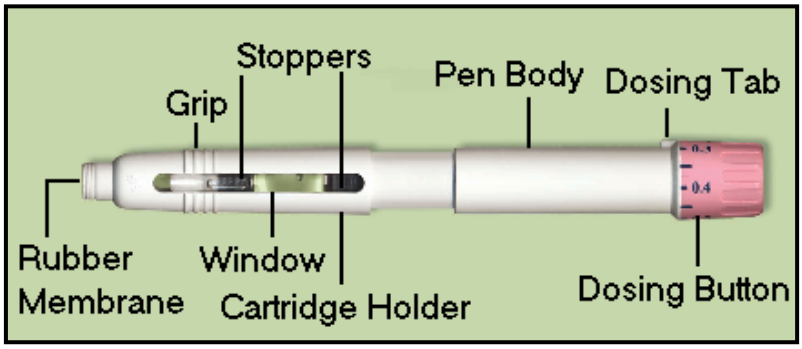
This leaflet was last approved on

ANNEX TO THE PACKAGE LEAFLET

How to use the PegIntron pre-filled pen





The following instructions explain how to inject yourself with the single use PegIntron pre-filled pen. **Please read the instructions carefully and completely before attempting to use the pen and follow them step by step.** Your doctor or his/her assistant will instruct you on how to self-inject with the PegIntron pre-filled pen. Do not attempt to inject yourself unless you are sure you understand the procedure and requirements for self-injection.

The PegIntron pre-filled pen is intended for use by one person only and must not be shared. Use the injection needle and cleansing swabs provided in the packaging only for the PegIntron pre-filled pen. Be sure the solution is at room temperature at the time of injection. Your doctor will have told you what dose you require for your therapy.

Note: The colour of the dosing button is different for each strength of the PegIntron pre-filled pen.

Step 1: Mixing

It is important that you keep the PegIntron pre-filled pen upright (as shown in figure 1) during mixing, unless otherwise instructed.

- Take the PegIntron pre-filled pen out of the refrigerator. Allow the medicine to come to room temperature.

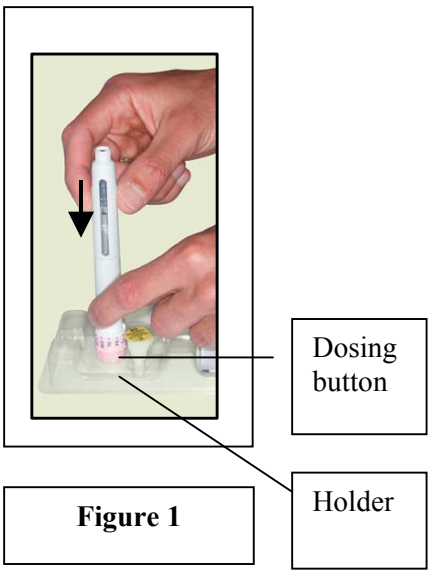
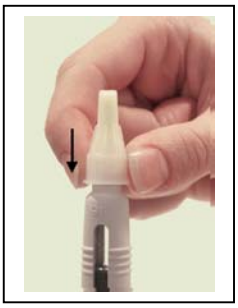


Figure 1

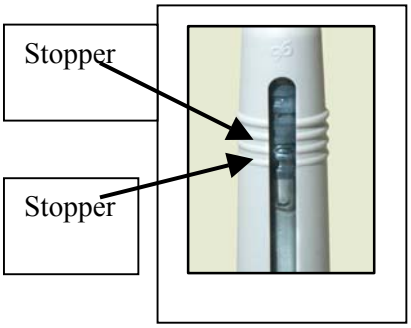
- Wash your hands with soap and water.
- **Place the PegIntron pre-filled pen upright** in the holder of the tray provided in the pack (the dosing button will be on the **bottom**).
- You may want to hold the pre-filled pen using the grip. To mix the powder and the liquid, press the two halves together firmly by pressing down until you hear the pre-filled pen click. The two stoppers should come together.
- Wait for several seconds until the powder is completely dissolved.
- **Gently turn the PegIntron pre-filled pen upside down twice. To avoid excessive foaming, do not shake.**
- Maintaining the PegIntron pre-filled pen upright, check the mixed PegIntron solution through the window. If there is still foam, wait until it settles. The solution should be clear and colourless. **Do not use the pen if the solution is discoloured or contains any particles.**



- Keeping the PegIntron pre-filled pen upright in the holder provided in the packaging, disinfect the rubber membrane of the PegIntron pre-filled pen with one cleansing swab.
- Take the injection needle provided in the tray and remove its protective paper tab.
- **Maintaining the PegIntron pre-filled pen upright in the holder,** gently push the injection needle onto the pre-filled pen and **screw it securely in place**.

Figure 2

- **Keep the PegIntron pre-filled pen pointed up**.
- **Do not take off the outer needle cap at this point.**
- You may see some liquid trickle out from under the cap, as the air has been expelled out of the pen.
- Wait about 5 seconds for this process to finish.



- **Check through the window to be sure that the two stoppers are together. If they are not together, do not use this pen because you may not be able to dial your dose.**

Figure 3

Step 2: Setting the dose

- Remove the PegIntron pre-filled pen from the holder.
- Holding the PegIntron pre-filled pen firmly, pull the dosing button out as far as it will go, until you see a **dark ring** on the pen. The dosing button should be easy to pull out without excessive force being required.

Note: Do not push the dosing button back in at this time. You will push it in when you are ready to self-inject the PegIntron.

Figure 4

Figure 5

- Turn the dosing button until your prescribed dose is aligned with the dosing tab. The button should turn easily without excessive force being required.

Note: **If you cannot easily pull out the dosing button or dial the dose, do not use excessive force and do not use this pen because it may not deliver the correct dose.**

Step 3: Injecting the solution

- Select the injection site. Your doctor will have told you which sites to use (e.g., thigh or abdomen).

Note: change your injection site each time.

- Clean the injection site skin with the second cleansing swab.

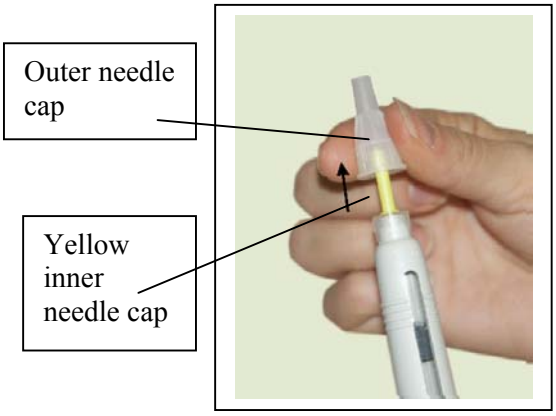


Figure 6

- Pull off the **outer needle cap**.
- There may be some liquid around the inner needle cap. This liquid is not part of your dose, this is extra. This is normal, as the air has been expelled out of the needle.
- Once the injection site is dry, pull off the **yellow inner needle cap** carefully exposing the injection needle.

Figure 7

- Hold the PegIntron pre-filled pen with your fingers wrapped around the barrel and your thumb on the dosing button.
- With your other hand, pinch a fold of loose skin.
- Insert the needle into the pinched skin at an angle of 45° to 90°.
- Press the dosing button down **slowly** and **firmly** until the button can no longer move.
- **Maintain pressure on the dosing button for an additional 5 seconds** to ensure that you get the complete dose.

- Remove the needle from your skin.
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- Discard the PegIntron pre-filled pen with the needle safely in a closed rigid container.

PACKAGE LEAFLET

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- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

In this leaflet:

PegIntron 150 micrograms powder and solvent for solution for injection in pre-filled pen
Peginterferon alfa-2b (conjugation of recombinant interferon alfa-2b with monomethoxy polyethylene glycol)

- The active substance is peginterferon alfa-2b, 150 micrograms/0.5 ml.
- The other ingredients are:
  Powder: disodium phosphate, anhydrous; sodium dihydrogen phosphate dihydrate, sucrose and polysorbate 80;
  Solvent: water for injections

Marketing Authorisation Holder: SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

Manufacturer: SP (Brinny) Company, Innishannon, County Cork, Ireland

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The pharmaceutical form is: powder and solvent for solution for injection.
The white powder and the clear and colourless solvent are both contained in a two-chamber glass cartridge assembled into a single use pre-filled pen.

PegIntron 150 micrograms is available in different pack sizes:
- 1 pen containing powder and solvent for solution for injection, 1 injection needle and 2 cleansing swabs;
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PegIntron is best used for this treatment in combination with ribavirin.

PegIntron is used alone in case of intolerance or contraindication to ribavirin.

2. BEFORE YOU USE PEGINTRON

PegIntron is not recommended for use in patients under the age of 18 years.

Do not use PegIntron:
- If you are hypersensitive (allergic) to peginterferon alfa-2b or any of the other ingredients of PegIntron.
- If you are hypersensitive (allergic) to any interferon.
- If you are pregnant or breast feeding.
- If you have had severe heart problems, or if you have heart disease that has not been well controlled during the past 6 months.
- If you have severe medical conditions that leave you very weak, including severe kidney disease.
- If you have autoimmune hepatitis or any other problem with your immune system; if you are taking medicine that suppresses your immune system (your immune system protects you against infection and some diseases).
- If you have advanced, uncontrolled liver disease (other than hepatitis C).
- If you have thyroid disease that is not well controlled with medicines.
- If you have a condition that causes convulsions (seizures, or "fits").

Take special care with PegIntron:
- If you develop symptoms of a severe allergic reaction (such as difficulty in breathing, wheezing, or hives) while on this medication, seek medical help immediately.
- If you ever had a heart attack or a heart problem.
- If you have ever been treated for depression or any other nervous or mental disorder.
- If you have had a problem with your liver (other than hepatitis C).
- If you develop symptoms associated with a cold or other respiratory infection, such as fever, cough, or any difficulty in breathing, tell your doctor.
- If you are diabetic, your doctor may ask you to have an eye examination.
- If you have had any serious illness affecting your breathing or your blood.
- If you have psoriasis, it may become worse while you are using PegIntron.
- If you are planning to become pregnant, discuss this with your doctor before starting to use PegIntron.
- If you are also being treated for HIV, please see **Using other medicines**.
- If you have had a severe nervous or mental disorder.
- If you have received an organ transplant, either kidney or liver, interferon treatment may increase the risk of rejection. Be sure to discuss this with your doctor.

While being treated with PegIntron
Your doctor may want you to drink extra fluids to help prevent low blood pressure.

Pregnancy
Ask your doctor or pharmacist for advice before taking any medicine. Do not use PegIntron during pregnancy. The effect on human pregnancy is not known.

Breast-feeding
Ask your doctor or pharmacist for advice before taking any medicine. It is not known whether this product is present in human milk. Therefore, do not breast-feed an infant if you are taking PegIntron.

Driving and using machines:
Do not drive or operate any tools or machines if you feel tired, sleepy or confused while taking PegIntron.

Using other medicines:
Please inform your doctor or pharmacist if you are taking or have recently taken any other medicines, even those not prescribed.

Important information about some of the ingredients of PegIntron:
This medicinal product contains less than 1 mmol sodium (23 mg) per 0.7 ml, i.e., essentially "sodium-free".

Patients who also have HIV infection:
Lactic acidosis and worsening liver function are side effects associated with Highly Active Anti-Retroviral Therapy (HAART), an HIV treatment. If you are receiving HAART, the addition of PegIntron and ribavirin may increase your risk of lactic acidosis and of liver failure. Your doctor will monitor you for signs and symptoms of these conditions. (Please be sure to read the ribavirin Patient Leaflet also).

3. HOW TO USE PEGINTRON

Your doctor has prescribed PegIntron specifically for you and your current condition; do not share this medicine with anyone else.

Your doctor has determined your dose of PegIntron based on your weight. If necessary, the dose may be changed during treatment.

Combination treatment
PegIntron, when given with ribavirin capsules, is usually given at a dose of 1.5 microgram/kg once a week.

Ribavirin capsules are taken every day, morning and evening. The number of ribavirin capsules you take depends on your weight.
- If you weigh less than 65 kg, take 2 capsules in the morning and 2 in the evening (total of 800 mg each day).
- If you weigh between 65 and 85 kg, take 2 capsules in the morning and 3 in the evening (total of 1,000 mg each day).
- If you weigh more than 85 kg, take 3 capsules in the morning and 3 in the evening (total 1,200 mg each day).

The combination treatment is continued for at least 6 months, and sometimes for one year.

PegIntron alone:
PegIntron, when given alone, is usually given at a dose of 0.5 or 1.0 microgram/kg once a week, for at least 6 months, and possibly for 1 year.

All patients:
If you are injecting PegIntron yourself, please be sure that the dose that has been prescribed for you is clearly provided on the package of medicine you receive.

If you have the impression that the effect of PegIntron is too strong or too weak, talk to your doctor or pharmacist.

PegIntron is intended for subcutaneous use. This means that it is injected through a short injection needle into the fatty tissue just under your skin. If you are injecting this medicine yourself, you will be instructed how to prepare and give the injection. Detailed instructions for subcutaneous administration are provided with this leaflet (see How to use the PegIntron pre-filled pen).

Prepare the dose just before you intend to inject it and use it immediately. Look carefully at the reconstituted solution prior to administration. Do not use if there is discolouration of the reconstituted solution or if particulate matter is present. PegIntron is intended for single use only. Thus, after you give yourself the injection, discard the PegIntron pre-filled pen with any solution that is left in it.

Inject PegIntron once each week on the same day. Injecting it at the same time of day each week will help you not to forget to take it.

Use PegIntron exactly as prescribed by your doctor. Do not exceed the recommended dosage, and take it for as long as prescribed.

If you use more PegIntron than you should:
Tell your doctor or healthcare professional as soon as possible.

If you forget to take PegIntron:
Take the dose as soon as you remember, then continue your treatment as usual.
Do not take a double dose to make up for forgotten individual doses. Contact your doctor or pharmacist if needed.

4. POSSIBLE SIDE EFFECTS

Like all medicines, PegIntron can have side effects. Although not all of these side effects may occur, they may need medical attention if they do.

Check with your doctor immediately if any of the following side effects occur: chest pain; changes in the way your heart beats; breathing problems, (including shortness of breath), confusion; feeling depressed, wanting to harm yourself, hallucinations, numbness or tingling feeling; dizziness, convulsion ("fit"); trouble sleeping, thinking or concentrating; difficulty remaining alert, severe stomach pain or cramps; blood or clots in stool (or black, tarry stool); fever or chills beginning after a few weeks of treatment, pain in your lower back or side; difficulty or inability to pass urine, painful or inflamed muscles (sometimes severe); problems with your eyes or your eyesight or hearing; severe or painful reddening of your skin or mucous membrane, severe bleeding from your nose. Your doctor will test your blood to ensure that your white blood cell (cells that fight infection) and red blood cell (cells that carry oxygen) counts, platelets (blood clotting cells) and other laboratory values are at acceptable levels.

Some people get depressed when taking PegIntron alone or in combination treatment with ribavirin, and in some cases people had suicidal thoughts or aggressive behaviour. Some patients have actually committed suicide. Be sure to seek emergency care if you notice that you are becoming depressed or have suicidal thoughts or change in your behaviour. You may want to consider asking a family member or close friend to help you stay alert to signs of depression or changes in your behaviour.

The most common side effects with the combination of PegIntron and ribavirin capsules are irritation or redness (and rarely, skin damage) at the site of injection, headache, tired feeling, shaking chills, fever, flu-like symptoms, weakness, loss of weight, nausea, loss of appetite, diarrhoea or loose stools, stomach pain, vomiting, muscle aches, pain in joints and muscles, feeling depressed, irritability, trouble falling asleep or staying asleep, feeling anxious or nervous, difficulty concentrating, mood swings, hair loss, itching, dry skin, sore throat, coughing, difficult breathing, dizziness, virus infection, rash, and dry mouth.

Other common side effects that may occur with combination treatment are increased sweating, chest pain, pain on the right side around your ribs, numbness, pain or tingling feeling, change in thyroid gland activity (which may make you feel tired or, less commonly, energetic), stomach upset, rapid heart rate, agitation, nervousness, difficult or irregular menstrual period.

Less common are pain at the place of injection, flushing, low or high blood pressure, dry or teary eyes, redness of skin or skin disorder, psoriasis, hives, nail disorder, feeling unwell, feeling faint, poor coordination, confusion, increased or decreased sensitivity to touch, tense muscles, arthritis, bruising, loss of interest in activities including sex, sexual problem, unusual dreams, shaky hands, vertigo (spinning feeling), increased appetite, heartburn, intestinal gas (flatus), constipation, hemorrhoids, red or bleeding gums, redness or sores in mouth, change in taste, changes in hearing or ringing in ears, thirst, aggressive or changed behaviour, feeling sleepy, cold sores, fungal or bacterial infections, irritation of prostate gland,

increased need to pass urine, ear or respiratory infections, sinusitis, stuffy or runny nose, abnormal hair texture, sensitivity to sunlight, migraine headache, eye pain or infection, blurred vision, puffy face, puffy hands or feet, enlarged liver, problem affecting ovary or vagina, pain in breast, difficulty in speaking, diabetes and swollen glands.

Very rarely sarcoidosis (a disease characterised by persistent fever, weight loss, joint pain and swelling, skin lesions and swollen glands) has been reported. Loss of consciousness has occurred very rarely with alpha interferons, mostly in elderly patients treated at high doses. Cases of stroke (cerebrovascular events) have been reported. Check with your doctor immediately if you have any of these symptoms or any other symptoms that are troubling.

Very rarely, PegIntron alone or in combination with ribavirin may cause aplastic anaemia.

When PegIntron is used alone, some of these effects are less likely to occur, and some have not occurred at all.

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

5. STORING PEGINTRON

Keep out of the reach and sight of children.

Store in a refrigerator (2°C - 8°C). Do not freeze.

Do not use after the expiry date stated on the carton.
After reconstitution, use the reconstituted solution immediately or within 24 hours when stored at 2°C - 8°C (in a refrigerator).

Do not use PegIntron if you notice discolouration of the reconstituted solution.

6. FURTHER INFORMATION

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

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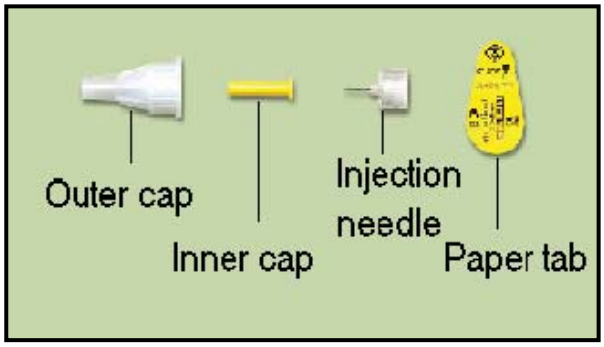
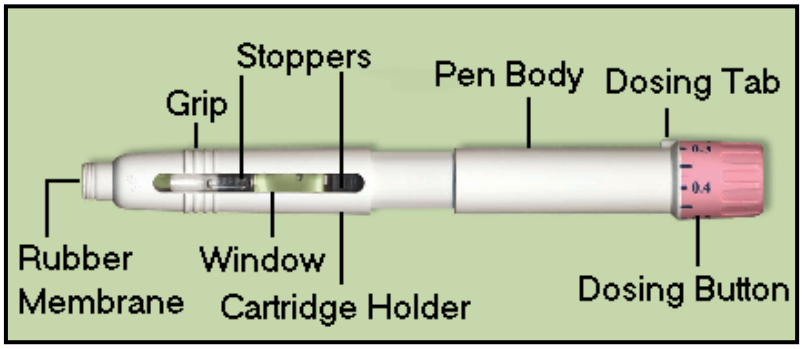
This leaflet was last approved on

ANNEX TO THE PACKAGE LEAFLET

How to use the PegIntron pre-filled pen





The following instructions explain how to inject yourself with the single use PegIntron pre-filled pen. **Please read the instructions carefully and completely before attempting to use the pen and follow them step by step.** Your doctor or his/her assistant will instruct you on how to self-inject with the PegIntron pre-filled pen. Do not attempt to inject yourself unless you are sure you understand the procedure and requirements for self-injection.

The PegIntron pre-filled pen is intended for use by one person only and must not be shared. Use the injection needle and cleansing swabs provided in the packaging only for the PegIntron pre-filled pen. Be sure the solution is at room temperature at the time of injection. Your doctor will have told you what dose you require for your therapy.

Note: The colour of the dosing button is different for each strength of the PegIntron pre-filled pen.

Step 1: Mixing

It is important that you keep the PegIntron pre-filled pen upright (as shown in figure 1) during mixing, unless otherwise instructed.

- Take the PegIntron pre-filled pen out of the refrigerator. Allow the medicine to come to room temperature.

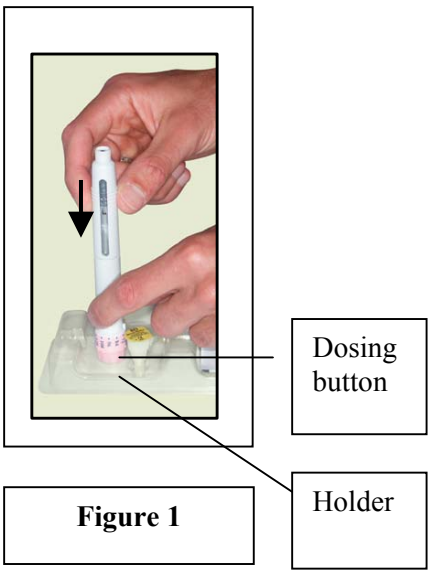
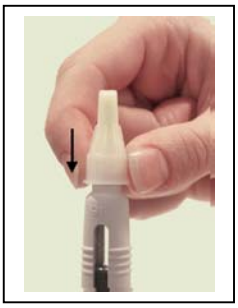


Figure 1

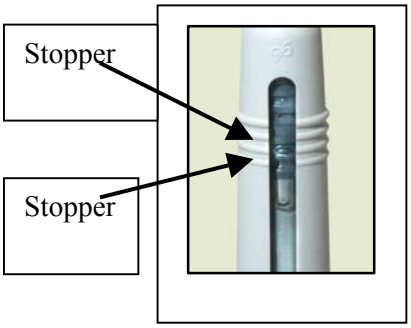
- Wash your hands with soap and water.
- **Place the PegIntron pre-filled pen upright** in the holder of the tray provided in the pack (the dosing button will be on the **bottom**).
- You may want to hold the pre-filled pen using the grip. To mix the powder and the liquid, press the two halves together firmly by pressing down until you hear the pre-filled pen click. The two stoppers should come together.
- Wait for several seconds until the powder is completely dissolved.
- **Gently turn the PegIntron pre-filled pen upside down twice. To avoid excessive foaming, do not shake.**
- Maintaining the PegIntron pre-filled pen upright, check the mixed PegIntron solution through the window. If there is still foam, wait until it settles. The solution should be clear and colourless. **Do not use the pen if the solution is discoloured or contains any particles.**



- Keeping the PegIntron pre-filled pen upright in the holder provided in the packaging, disinfect the rubber membrane of the PegIntron pre-filled pen with one cleansing swab.
- Take the injection needle provided in the tray and remove its protective paper tab.
- **Maintaining the PegIntron pre-filled pen upright in the holder,** gently push the injection needle onto the pre-filled pen and **screw it securely in place**.

Figure 2

- **Keep the PegIntron pre-filled pen pointed up**.
- **Do not take off the outer needle cap at this point.**
- You may see some liquid trickle out from under the cap, as the air has been expelled out of the pen.
- Wait about 5 seconds for this process to finish.



- **Check through the window to be sure that the two stoppers are together. If they are not together, do not use this pen because you may not be able to dial your dose.**

Figure 3

Step 2: Setting the dose

- Remove the PegIntron pre-filled pen from the holder.
- Holding the PegIntron pre-filled pen firmly, pull the dosing button out as far as it will go, until you see a **dark ring** on the pen. The dosing button should be easy to pull out without excessive force being required.

Note: Do not push the dosing button back in at this time. You will push it in when you are ready to self-inject the PegIntron.

Figure 4

Figure 5

- Turn the dosing button until your prescribed dose is aligned with the dosing tab. The button should turn easily without excessive force being required.

Note: **If you cannot easily pull out the dosing button or dial the dose, do not use excessive force and do not use this pen because it may not deliver the correct dose.**

Step 3: Injecting the solution

- Select the injection site. Your doctor will have told you which sites to use (e.g., thigh or abdomen).

Note: change your injection site each time.

- Clean the injection site skin with the second cleansing swab.

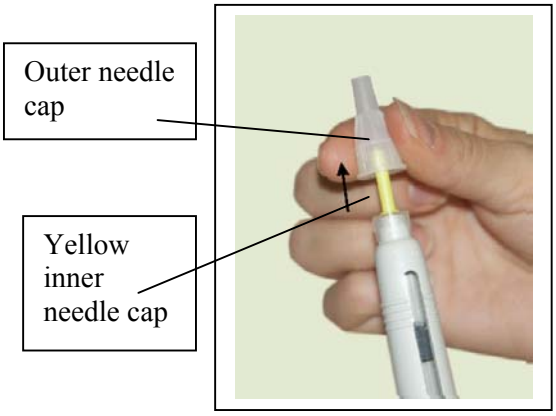


Figure 6

- Pull off the **outer needle cap**.
- There may be some liquid around the inner needle cap. This liquid is not part of your dose, this is extra. This is normal, as the air has been expelled out of the needle.
- Once the injection site is dry, pull off the **yellow inner needle cap** carefully exposing the injection needle.

Figure 7

- Hold the PegIntron pre-filled pen with your fingers wrapped around the barrel and your thumb on the dosing button.
- With your other hand, pinch a fold of loose skin.
- Insert the needle into the pinched skin at an angle of 45° to 90°.
- Press the dosing button down **slowly** and **firmly** until the button can no longer move.
- **Maintain pressure on the dosing button for an additional 5 seconds** to ensure that you get the complete dose.

- Remove the needle from your skin.
- Press the injection site with a small bandage or sterile gauze if necessary for a few seconds.
- Do not massage the injection site. If there is bleeding, cover with an adhesive bandage.
- Discard the PegIntron pre-filled pen with the needle safely in a closed rigid container.